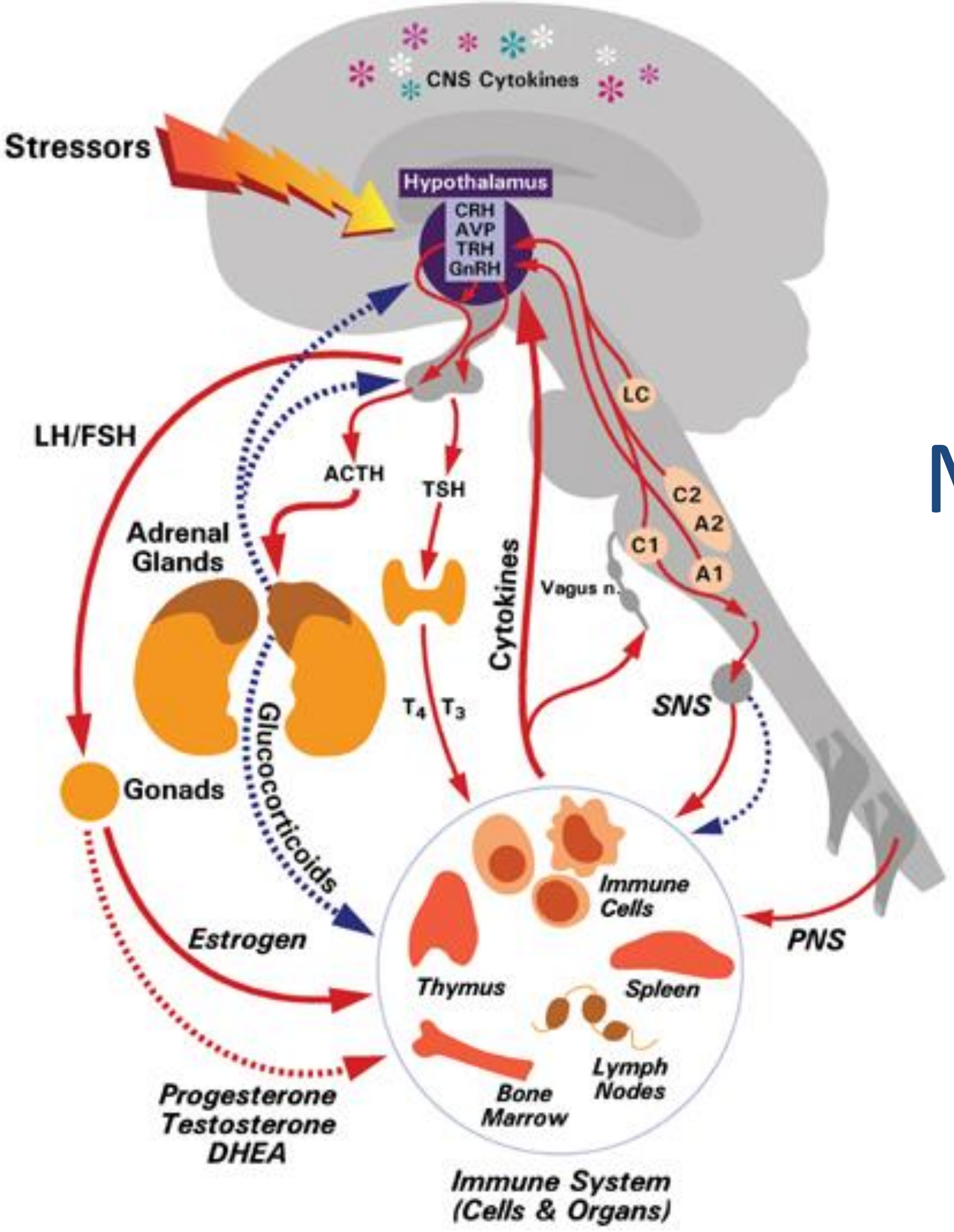
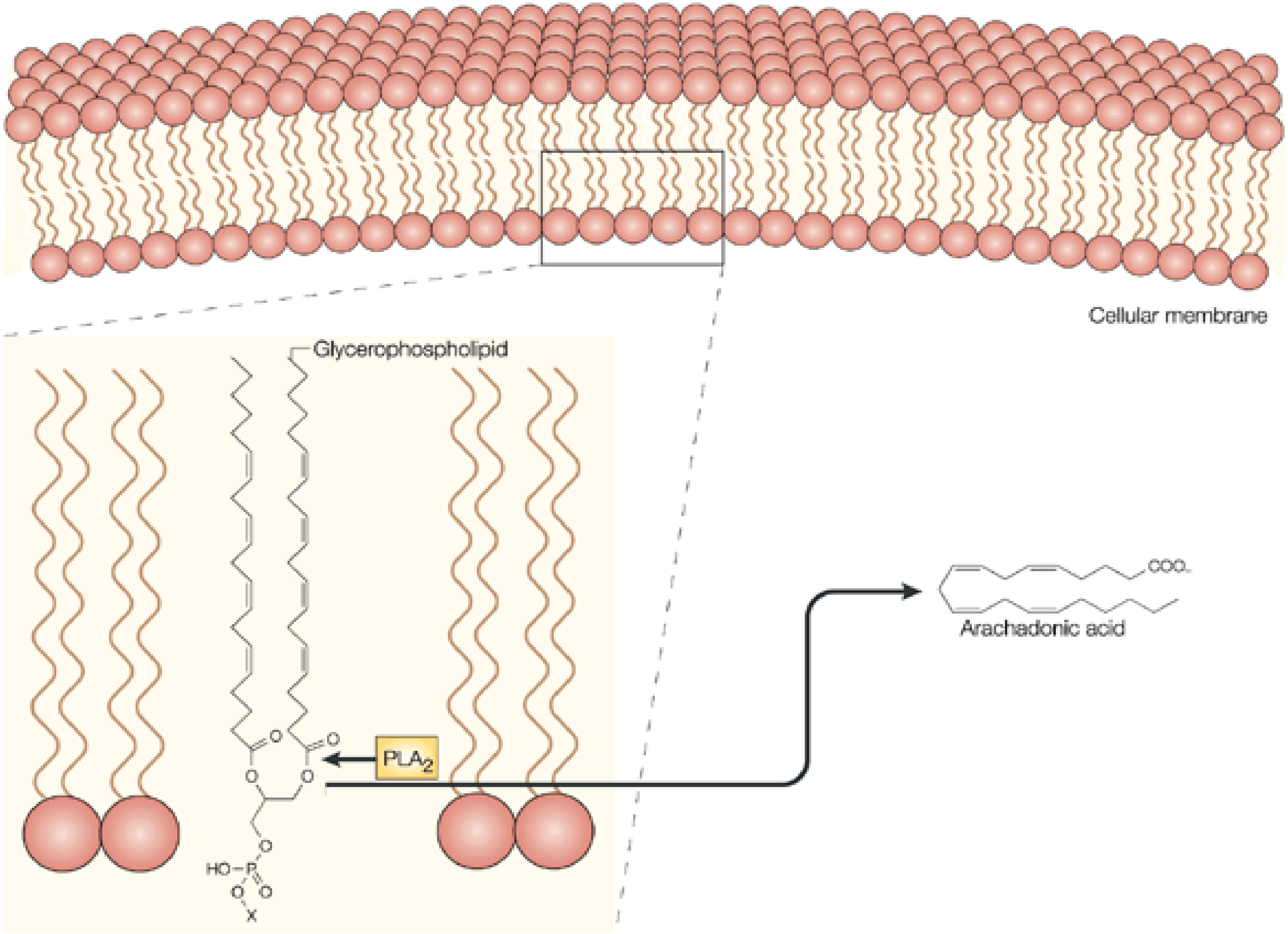
Neuroimunoendocrinologia


CNS Cytokines
Stressors
Hypothalamus
CRH
AVP
TRH
GnRH
LH/FSH
ACTH
TSH
LC
C2
A2
C1
A1
Adrenal Glands
Cytokines
Vagus n.
T4 T3
SNS
Gonads
Glucocorticoids
Immune Cells
Thymus
Spleen
Estrogen
PNS
Lymph Nodes
Bone Marrow
Progesterone
Testosterone
DHEA
Immune System (Cells & Organs)

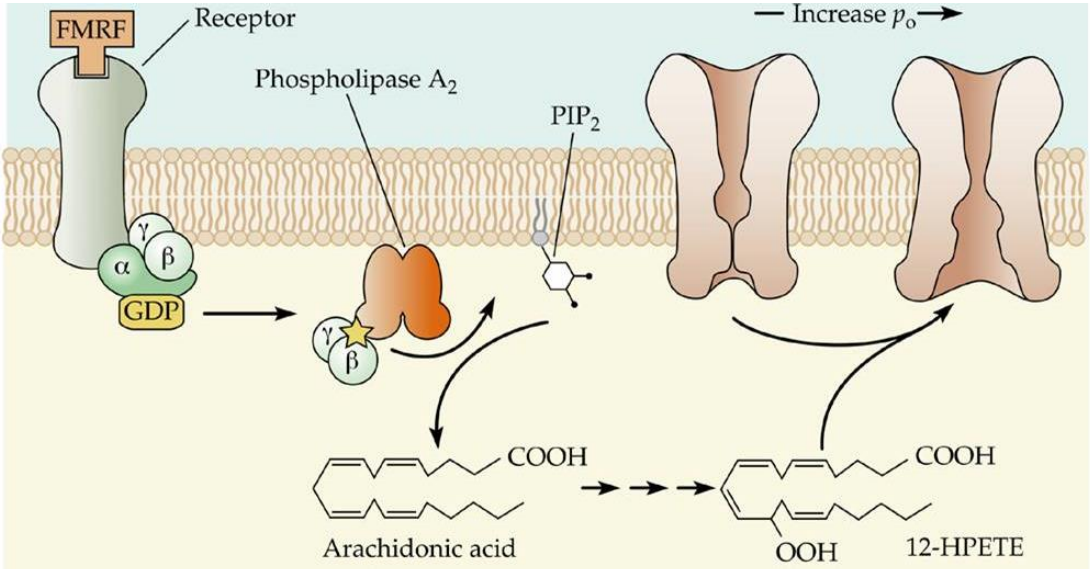
Mediadores Lipídicos

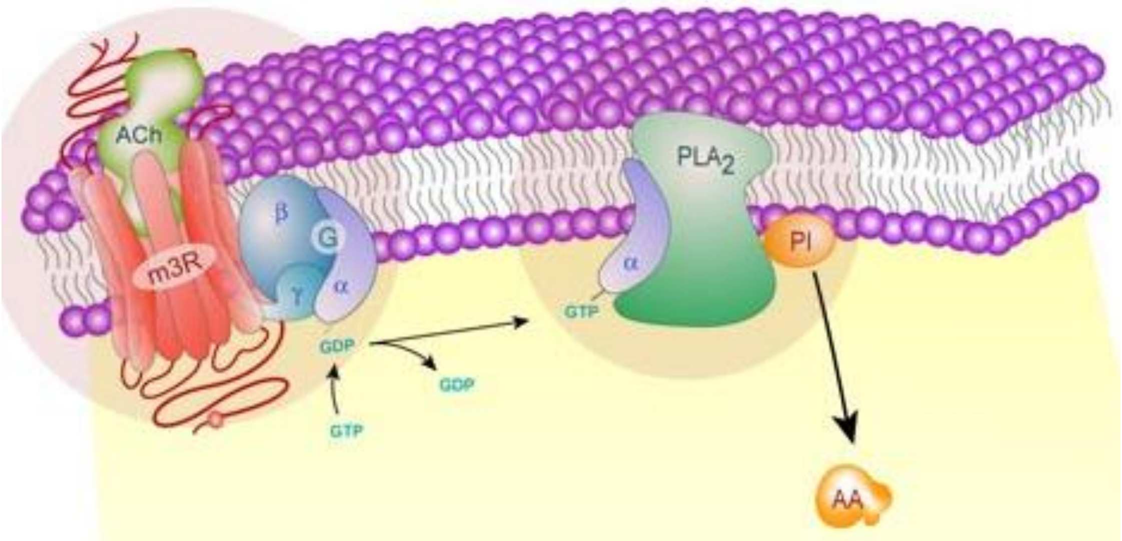
Pedro Augusto Carlos Magno Fernandes
Departamento de Fisiologia, sala 317.
e-mail: pacmf@usp.br

Mediadores Lipídicos

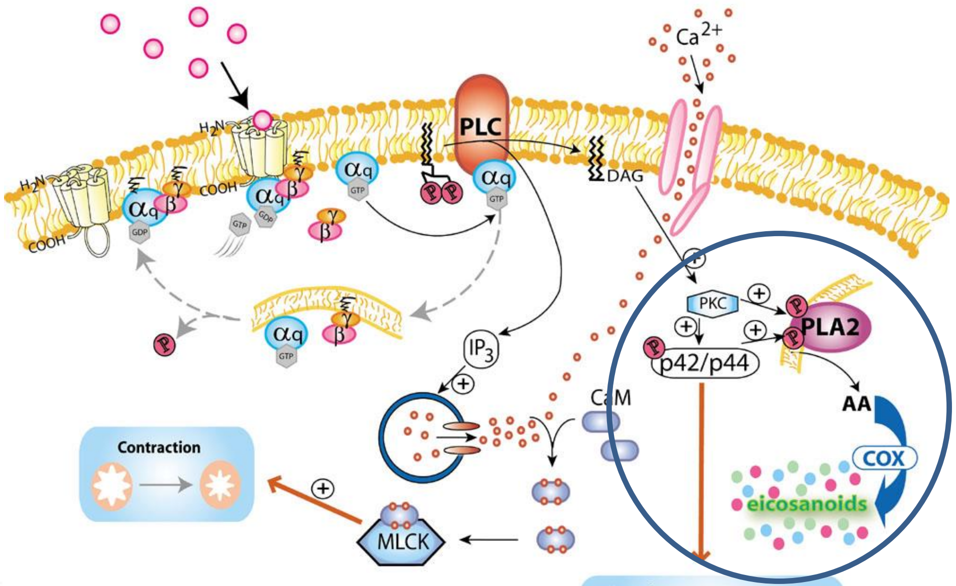

Cellular membrane
Glycerophospholipid
PLA2
HO–P
O
X
COO-
Arachadonic acid

Ativação da PLA2

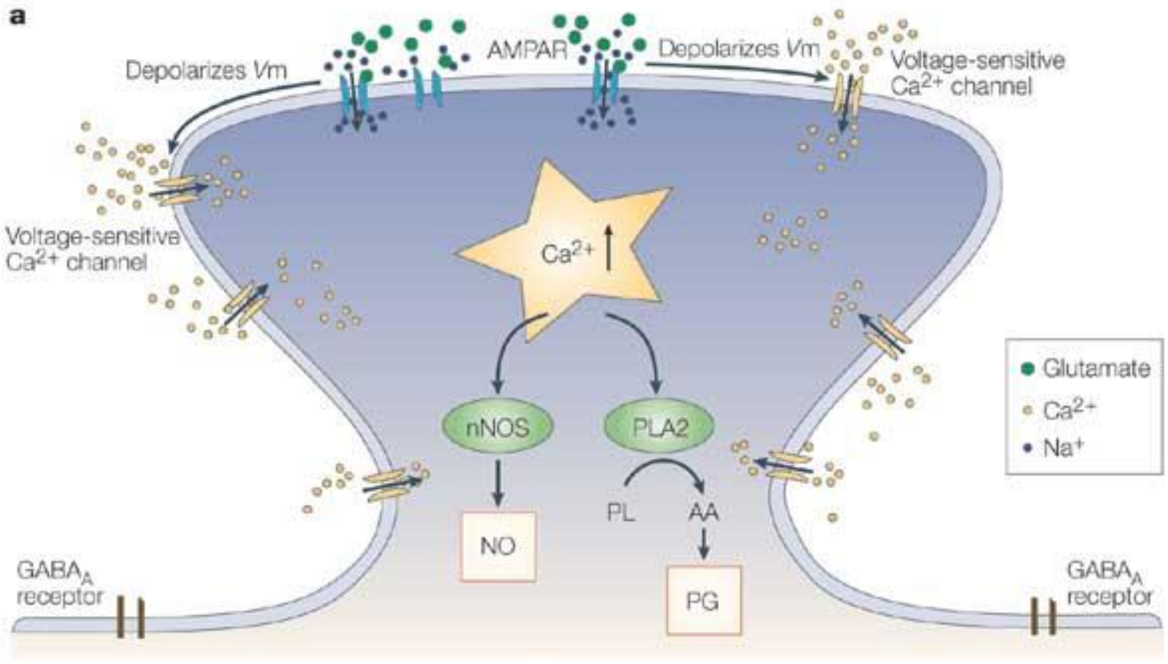

FMRF
Receptor
Phospholipase A_2
PIP_2
— Increase p_o →
γ
β
α
GDP
γ
β
COOH
Arachidonic acid
COOH
OOH
12-HPETE


ACh
m3R
β
G
γ
α
GDP
GTP
GDP
PLA_2
α
GTP
PI
AA

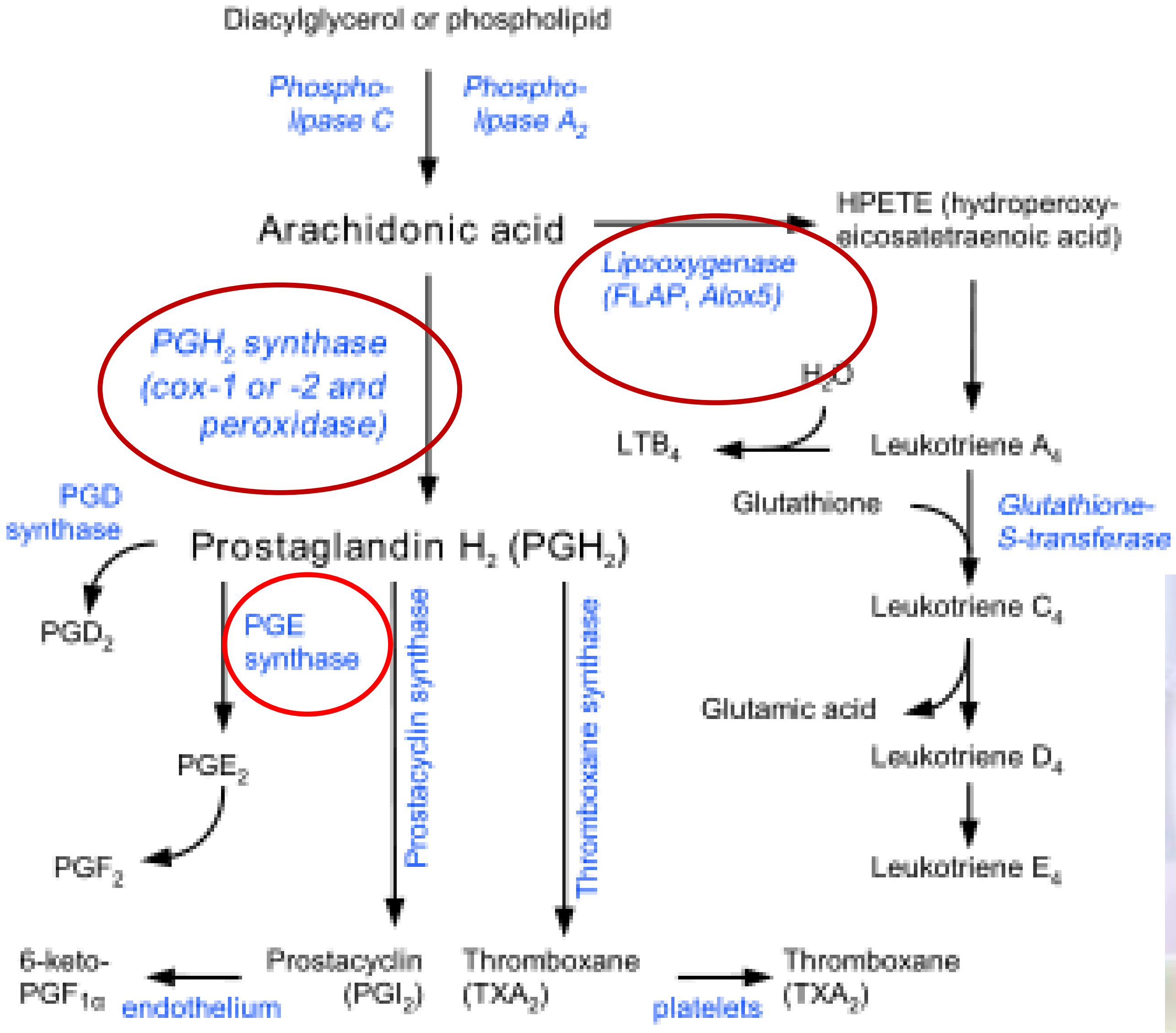
Ativação da PLA2

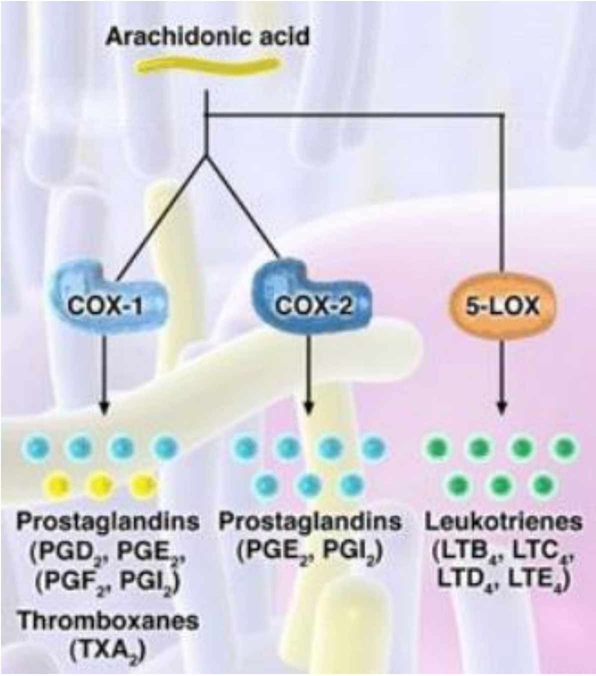

Ca2+
H2N
COOH
H2N
COOH
αq
β
γ
GDP
GTP
αq
GTP
PLC
DAG
IP3
+
CaM
Contraction
MLCK
PKC
PLA2
p42/p44
AA
COX
eicosanoids
Growth

Respiratory Research


a
Depolarizes Vm
AMPAR
Depolarizes Vm
Voltage-sensitive Ca2+ channel
Voltage-sensitive Ca2+ channel
Ca2+ ↑
nNOS
PLA2
PL
AA
NO
PG
GABAA receptor
GABAA receptor
Glutamate
Ca2+
Na+

Transformação do àcido araquidônico

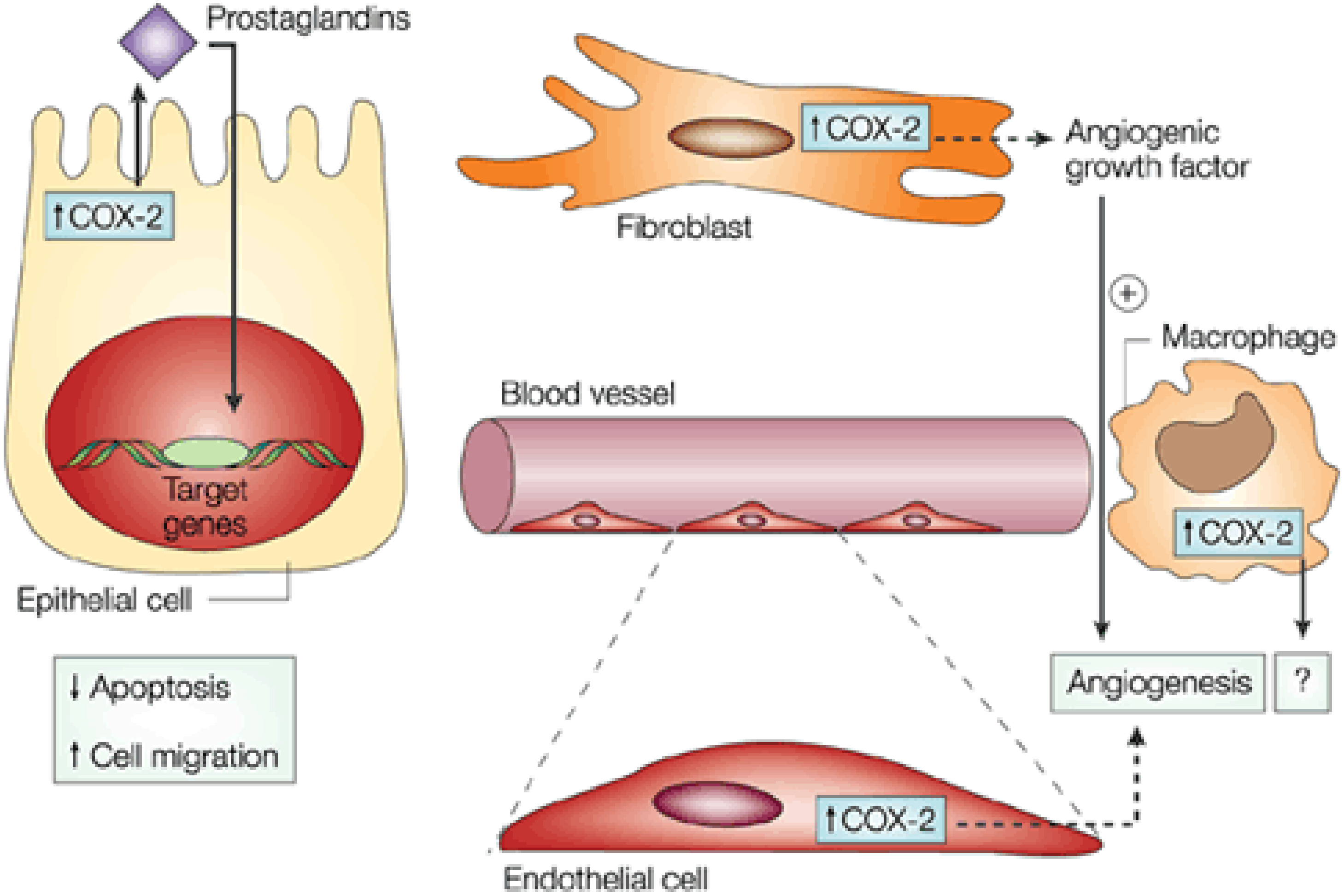

Diacylglycerol or phospholipid
Phospholipase C
Phospholipase A_2
Arachidonic acid
Lipooxygenase (FLAP, Alox5)
HPETE (hydroperoxy-eicosatetraenoic acid)
PGH_2 synthase (cox-1 or -2 and peroxidase)
H_2O
LTB_4
Leukotriene A_4
Glutathione
Glutathione-S-transferase
PGD synthase
Prostaglandin H_2 (PGH_2)
PGD_2
PGE synthase
Prostacyclin synthase
Thromboxane synthase
Leukotriene C_4
Glutamic acid
Leukotriene D_4
PGE_2
PGF_2
Leukotriene E_4
6-keto-$PGF_{1\alpha}$
endothelium
Prostacyclin (PGI_2)
Thromboxane (TXA_2)
platelets
Thromboxane (TXA_2)


Arachidonic acid
COX-1
COX-2
5-LOX
Prostaglandins (PGD_2, PGE_2, (PGF_2, PGI_2)
Thromboxanes (TXA_2)
Prostaglandins (PGE_2, PGI_2)
Leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4)

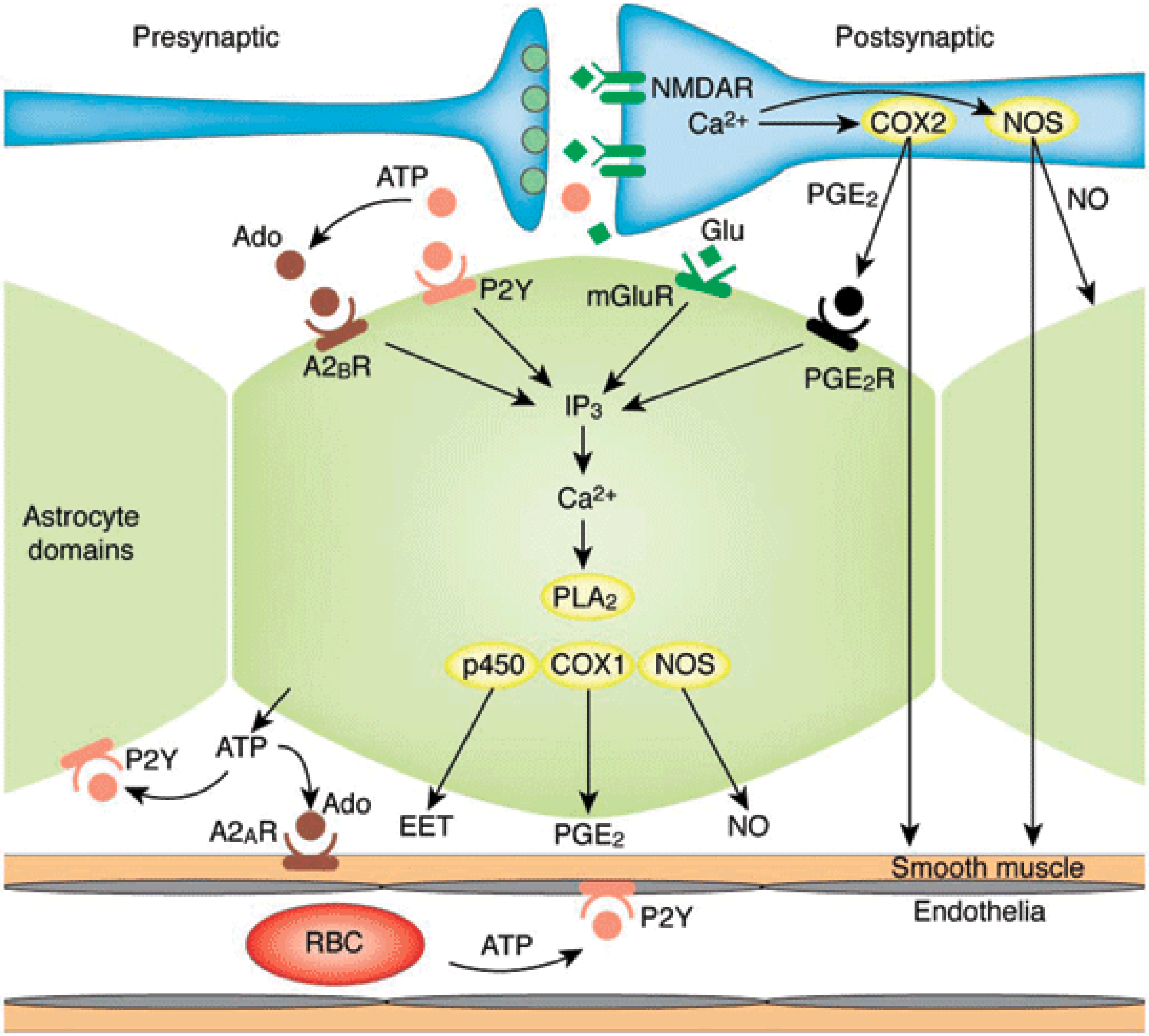
Ciclooxigenases

COX1: constitutiva na maioria dos tecidos (microglia)

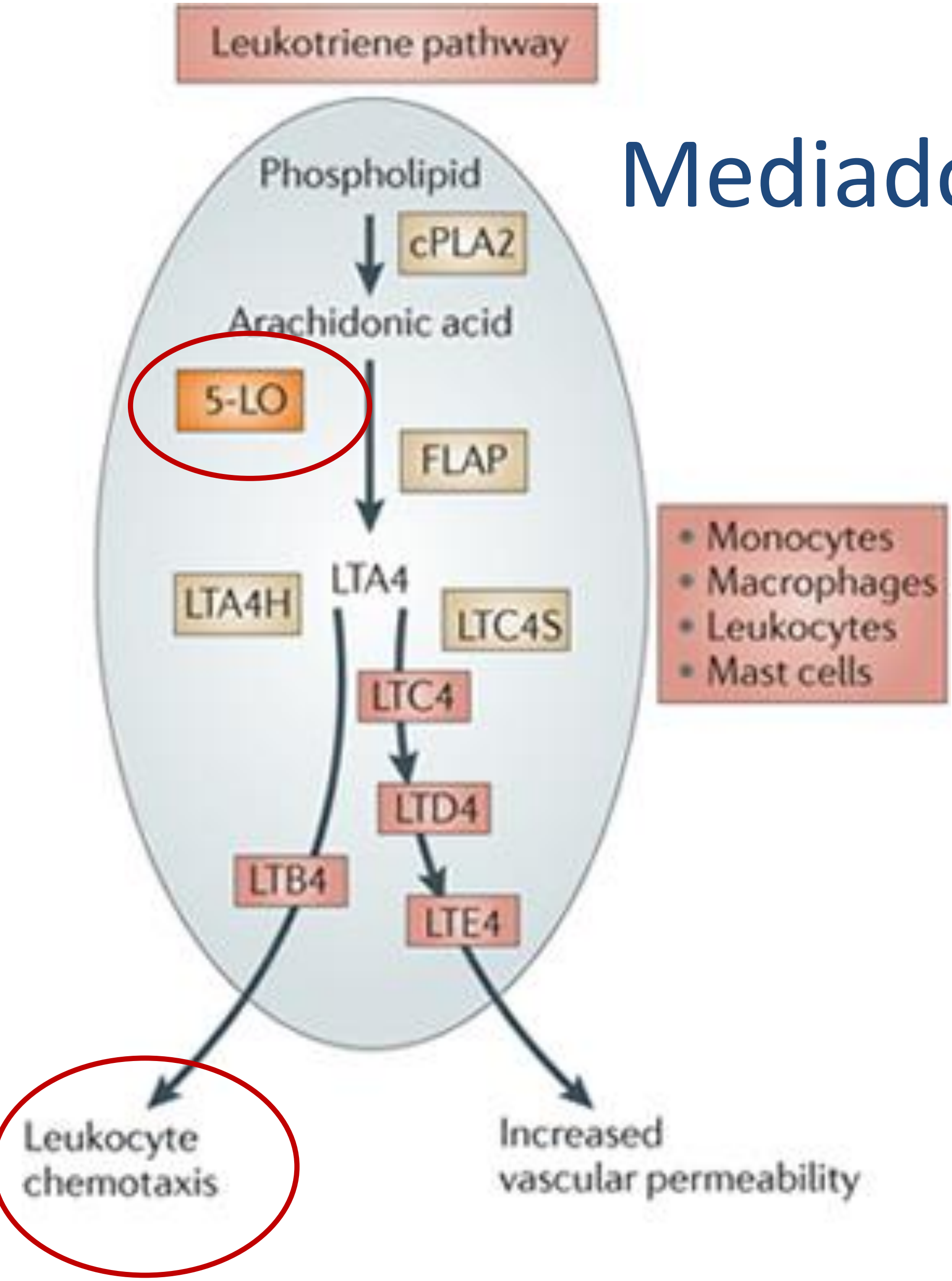
COX2: induzida (constitutiva em neurônios; coração)


Prostaglandins
↑COX-2
Target genes
Epithelial cell
↓ Apoptosis
↑ Cell migration
↑COX-2
Fibroblast
Angiogenic growth factor
+
Macrophage
↑COX-2
Blood vessel
Angiogenesis
?
↑COX-2
Endothelial cell

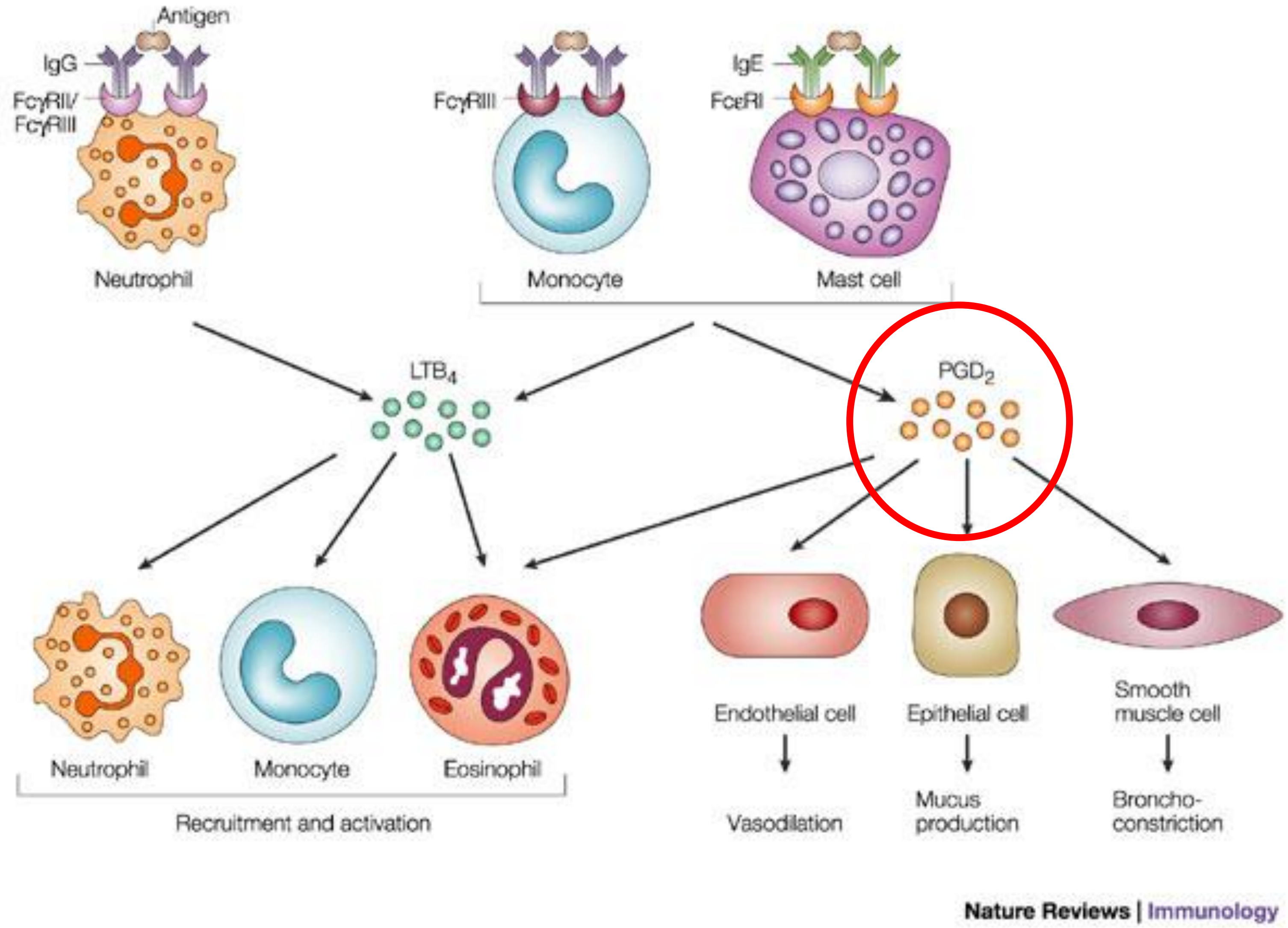
Neuroimunomodulação


Presynaptic
Postsynaptic
NMDAR
Ca^{2+}
COX2
NOS
ATP
Ado
PGE_2
NO
Glu
P2Y
mGluR
$A2_BR$
PGE_2R
IP_3
Ca^{2+}
Astrocyte domains
PLA_2
p450
COX1
NOS
P2Y
ATP
Ado
$A2_AR$
EET
PGE_2
NO
Smooth muscle
Endothelia
RBC
ATP
P2Y

Mediadores Lipídicos - Ações

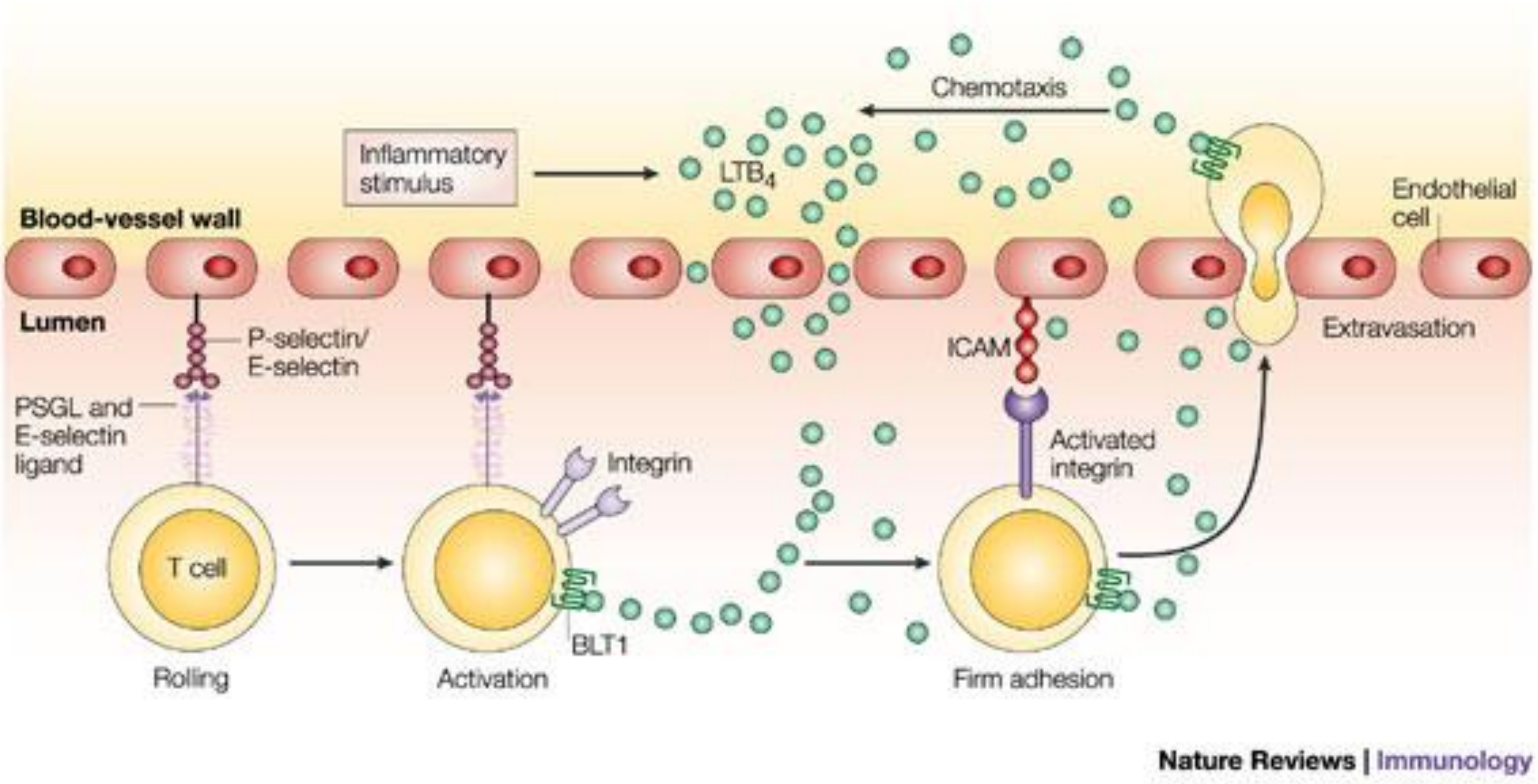

Leukotriene pathway
Phospholipid
cPLA2
Arachidonic acid
5-LO
FLAP
LTA4
LTA4H
LTC4S
LTC4
LTD4
LTB4
LTE4
Monocytes
Macrophages
Leukocytes
Mast cells
Leukocyte chemotaxis
Increased vascular permeability

Mediadores Lipídicos - Ações


Antigen
IgG
FcγRII/
FcγRIII
Neutrophil
FcγRIII
Monocyte
IgE
FcεRI
Mast cell
LTB4
PGD2
Neutrophil
Monocyte
Eosinophil
Recruitment and activation
Endothelial cell
Vasodilation
Epithelial cell
Mucus production
Smooth muscle cell
Broncho-constriction
Nature Reviews | Immunology

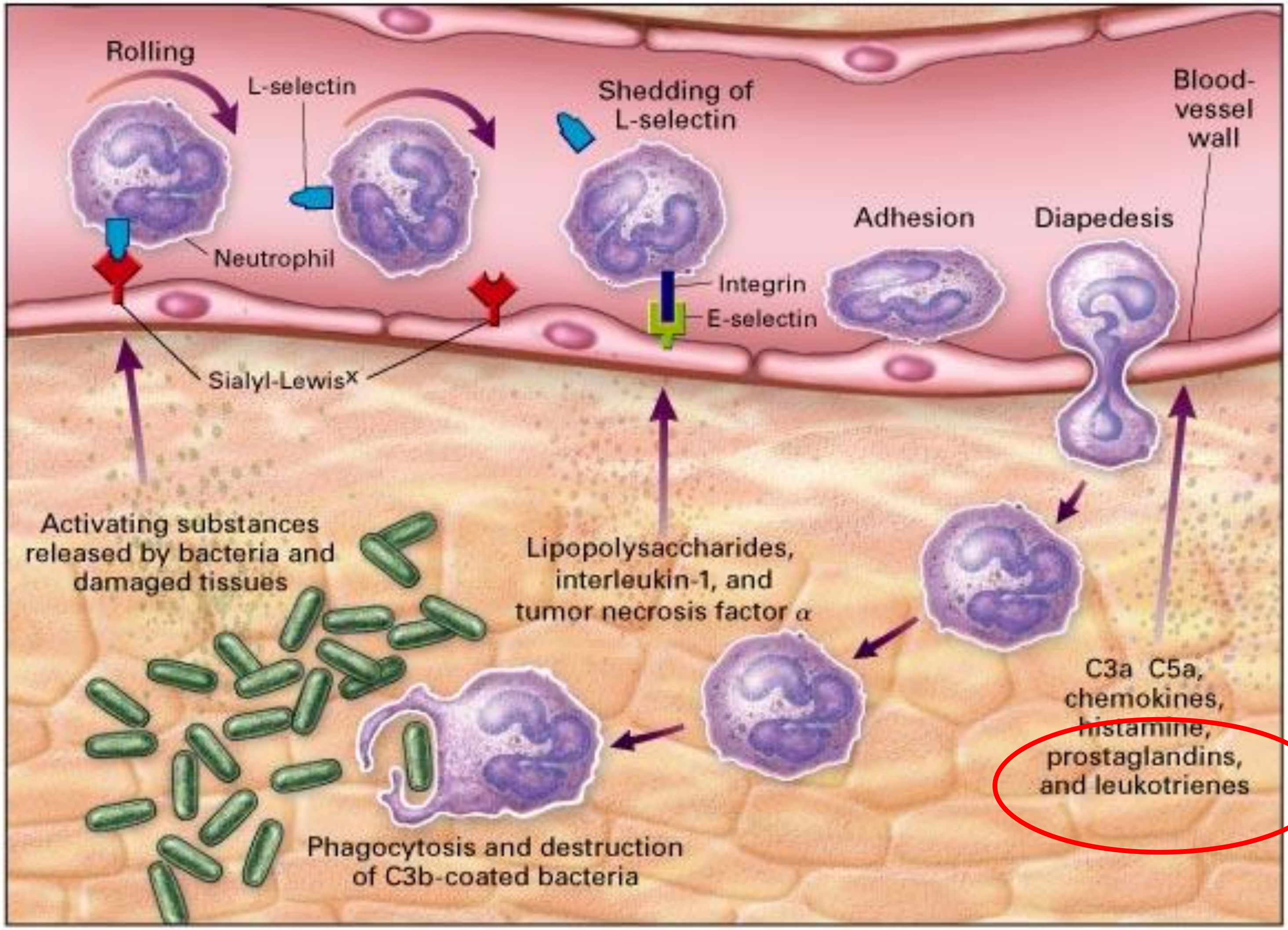
T-cell trafficking in asthma: lipid mediators grease the way
Andrew D. Luster & Andrew M. Tager Nature Reviews Immunology 4, 711-724 (September 2004)

Mediadores Lipídicos - Ações

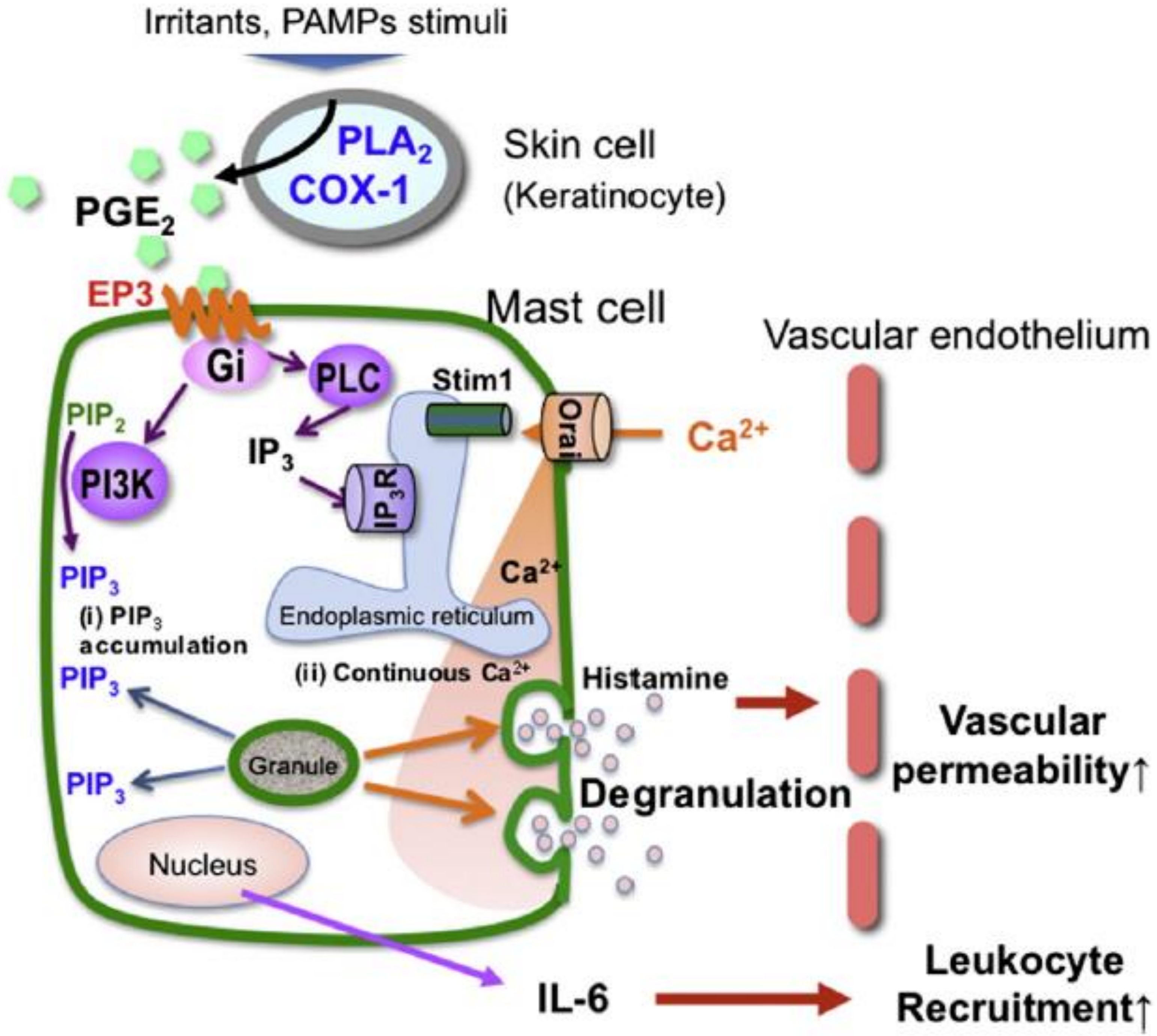

Chemotaxis
Inflammatory stimulus
LTB4
Blood-vessel wall
Endothelial cell
Lumen
P-selectin/ E-selectin
PSGL and E-selectin ligand
ICAM
Extravasation
Activated integrin
Integrin
T cell
BLT1
Rolling
Activation
Firm adhesion

Nature Reviews | Immunology

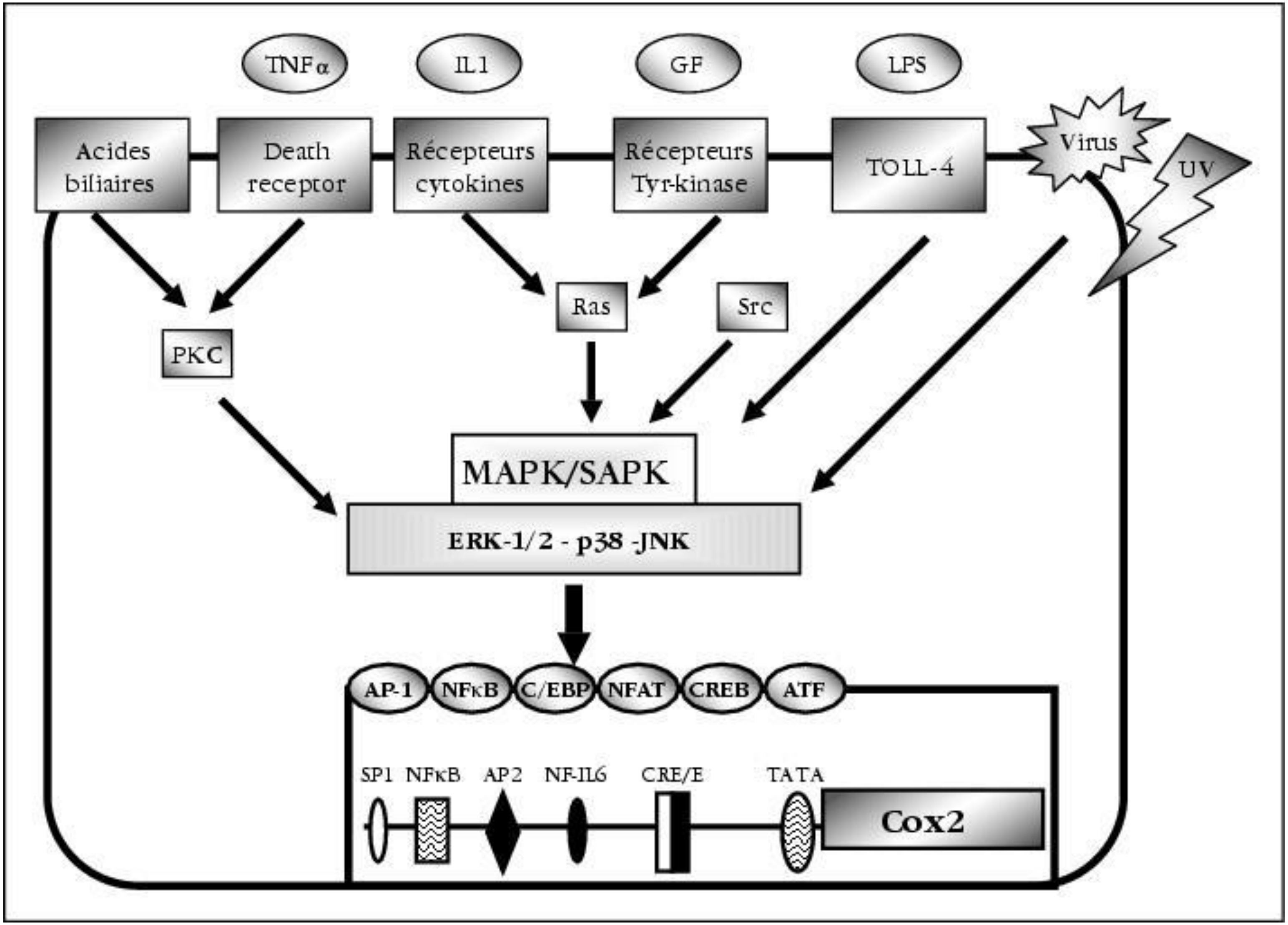
Resposta imune inata


Rolling
L-selectin
Shedding of L-selectin
Blood-vessel wall
Adhesion
Diapedesis
Neutrophil
Integrin
E-selectin
Sialyl-Lewis^x
Activating substances released by bacteria and damaged tissues
Lipopolysaccharides, interleukin-1, and tumor necrosis factor α
C3a C5a, chemokines, histamine, prostaglandins, and leukotrienes
Phagocytosis and destruction of C3b-coated bacteria

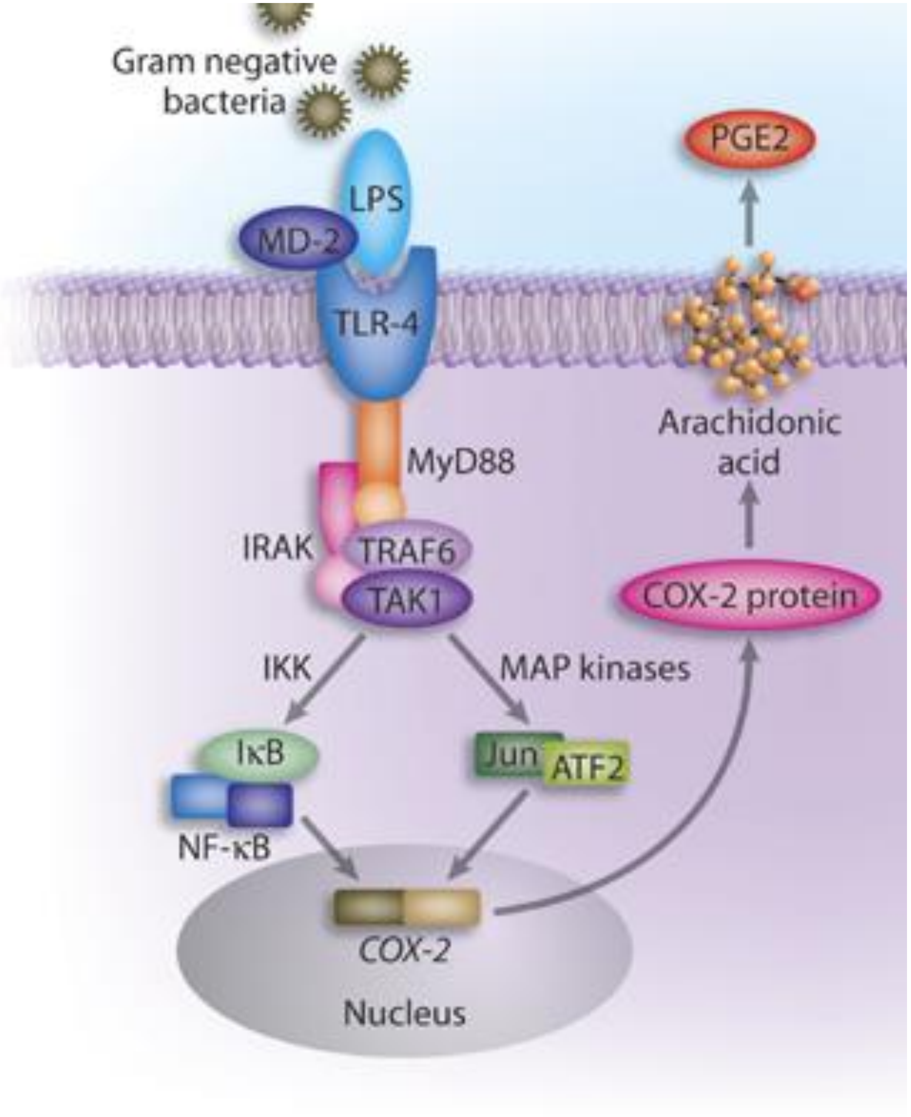
http://2.bp.blogspot.com/-Gufy8c9x07o/UJXVOdoMauI/AAAAAAAAQkY/Ql2N1Ye5gjg/s1600/rolling.jpg

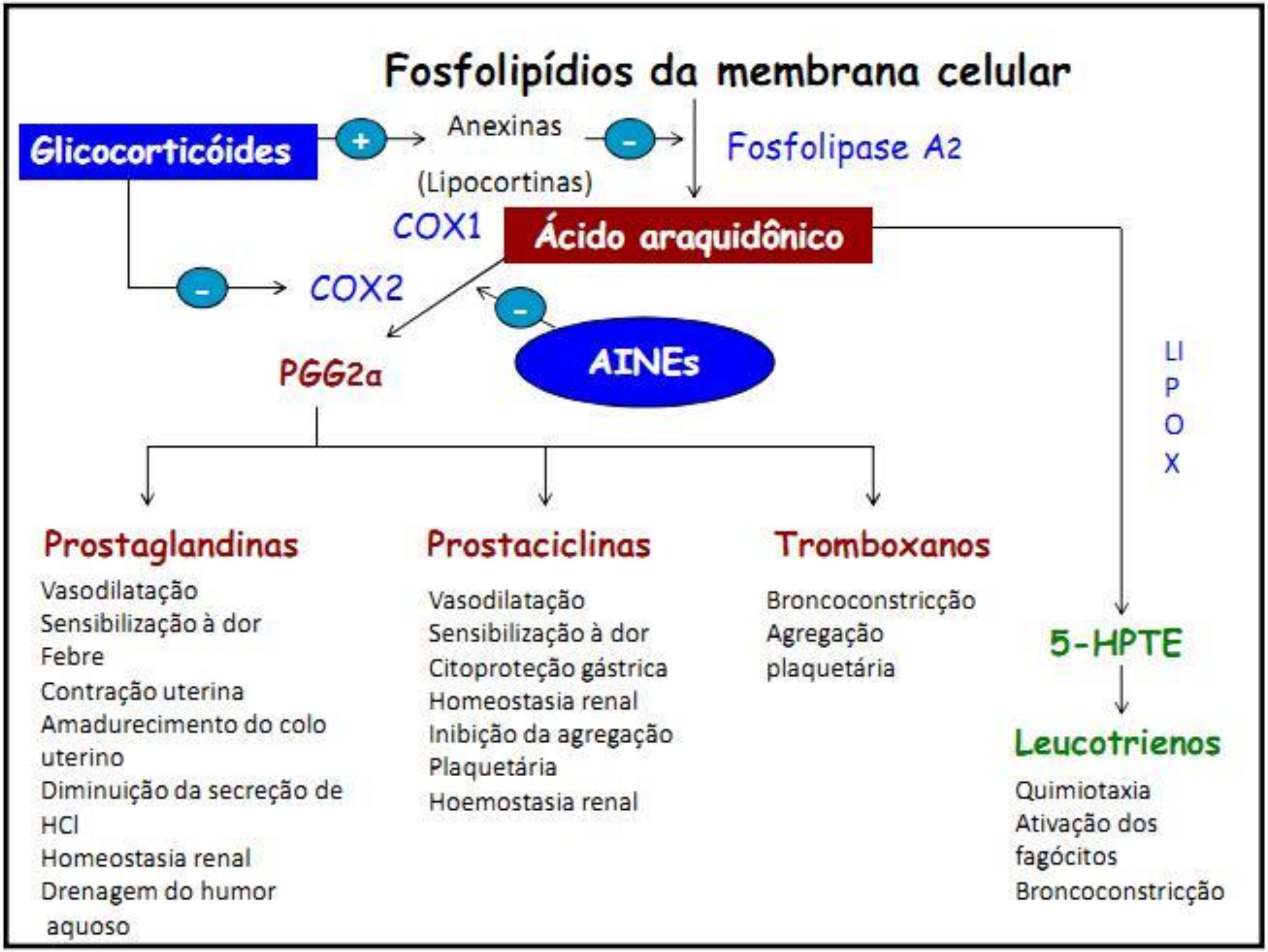

Irritants, PAMPs stimuli
PLA_2
COX-1
Skin cell
(Keratinocyte)
PGE_2
EP3
Mast cell
Gi
PLC
Stim1
Orai
Ca^{2+}
Vascular endothelium
PIP_2
PI3K
IP_3
IP_3R
PIP_3
(i) PIP_3 accumulation
Ca^{2+}
Endoplasmic reticulum
(ii) Continuous Ca^{2+}
PIP_3
Histamine
Granule
PIP_3
Degranulation
Vascular permeability↑
Nucleus
IL-6
Leukocyte Recruitment↑

Ciclooxigenase


TNFα
IL1
GF
LPS
Acides biliaires
Death receptor
Récepteurs cytokines
Récepteurs Tyr-kinase
TOLL-4
Virus
UV
Ras
Src
PKC
MAPK/SAPK
ERK-1/2 - p38 -JNK
AP-1
NFκB
C/EBP
NFAT
CREB
ATF
SP1
NFκB
AP2
NF-IL6
CRE/E
TATA
Cox2

Ciclooxigenase


Gram negative bacteria
LPS
MD-2
TLR-4
MyD88
IRAK
TRAF6
TAK1
IKK
MAP kinases
IκB
NF-κB
Jun
ATF2
COX-2
Nucleus
COX-2 protein
Arachidonic acid
PGE2



Fosfolipídios da membrana celular

Glicocorticóides

+ Anexinas (Lipocortinas)

-

Fosfolipase A2

COX1

Ácido araquidônico

- COX2

-

AINEs

PGG2a

LI
P
O
X

Prostaglandinas

Vasodilatação
Sensibilização à dor
Febre
Contração uterina
Amadurecimento do colo uterino
Diminuição da secreção de HCl
Homeostasia renal
Drenagem do humor aquoso

Prostaciclinas

Vasodilatação
Sensibilização à dor
Citoproteção gástrica
Homeostasia renal
Inibição da agregação Plaquetária
Hoemostasia renal

Tromboxanos

Broncoconstricção
Agregação plaquetária

5-HPTE

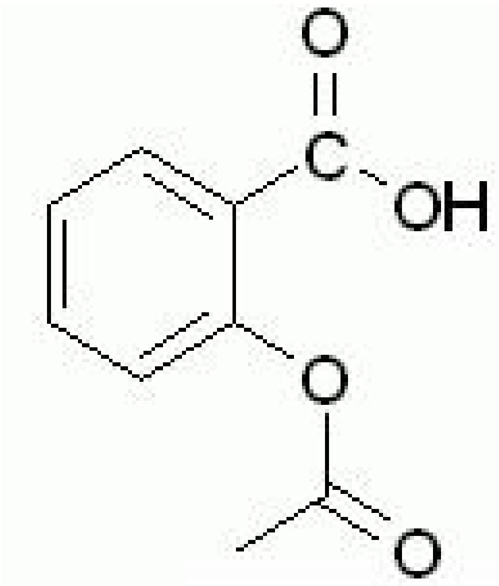
Leucotrienos

Quimiotaxia
Ativação dos fagócitos
Broncoconstricção

AINEs

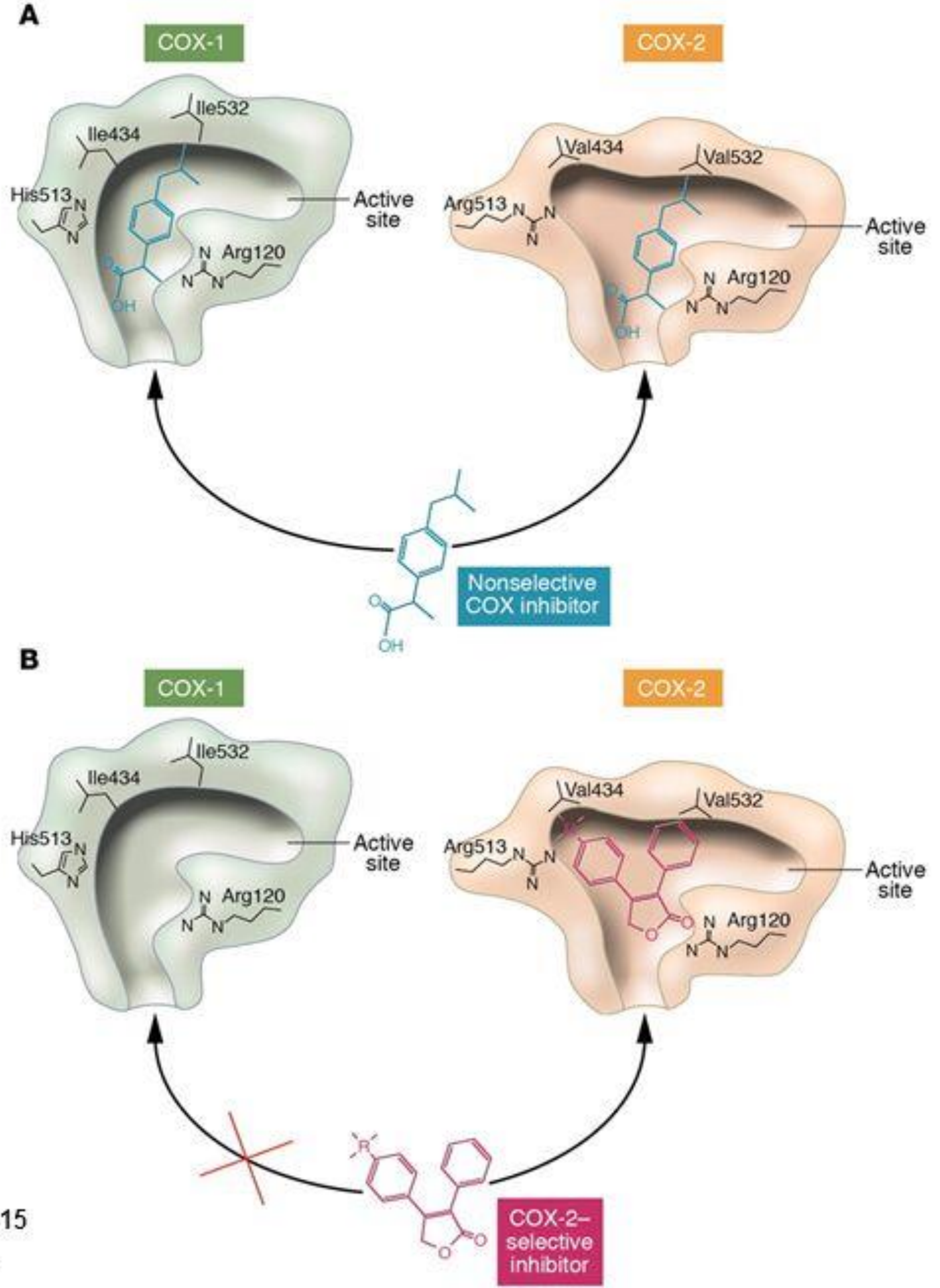
Anti-inflamatórios não esteroidais

ASPIRINA
0,5



ácido acetil-salicílico (Aspirina)

Schematic depiction of the structural differences between the substrate-binding channels of COX-1 and COX-2 that allowed the design of selective inhibitors


A
COX-1
COX-2
Ile532
Ile434
His513
Active site
Arg120
Val434
Val532
Arg513
Active site
Arg120
Nonselective COX inhibitor
B
COX-1
COX-2
Ile532
Ile434
His513
Active site
Arg120
Val434
Val532
Arg513
Active site
Arg120
R
COX-2–selective inhibitor

Grosser, T. et al. J. Clin. Invest. 2006;116:4-15

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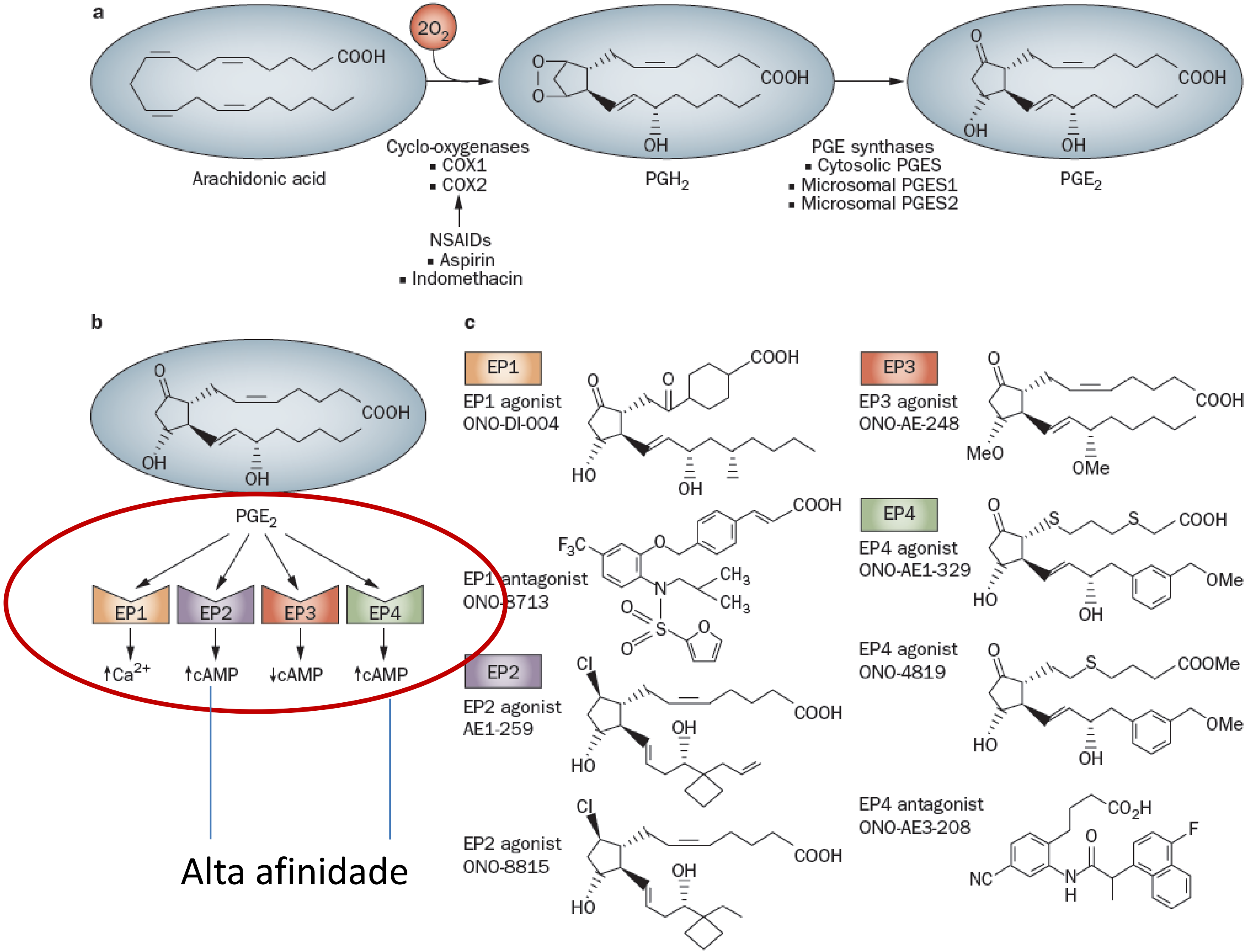
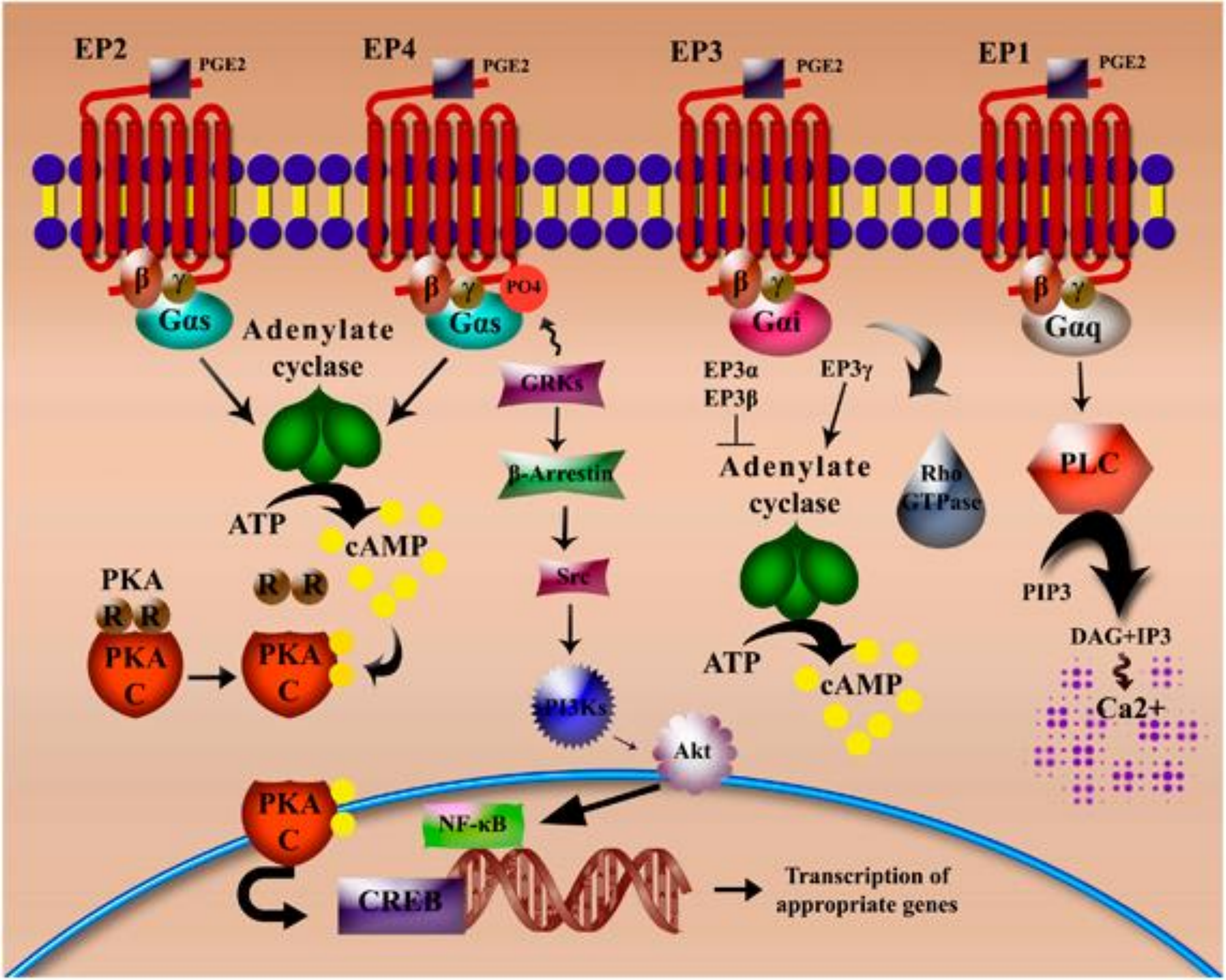
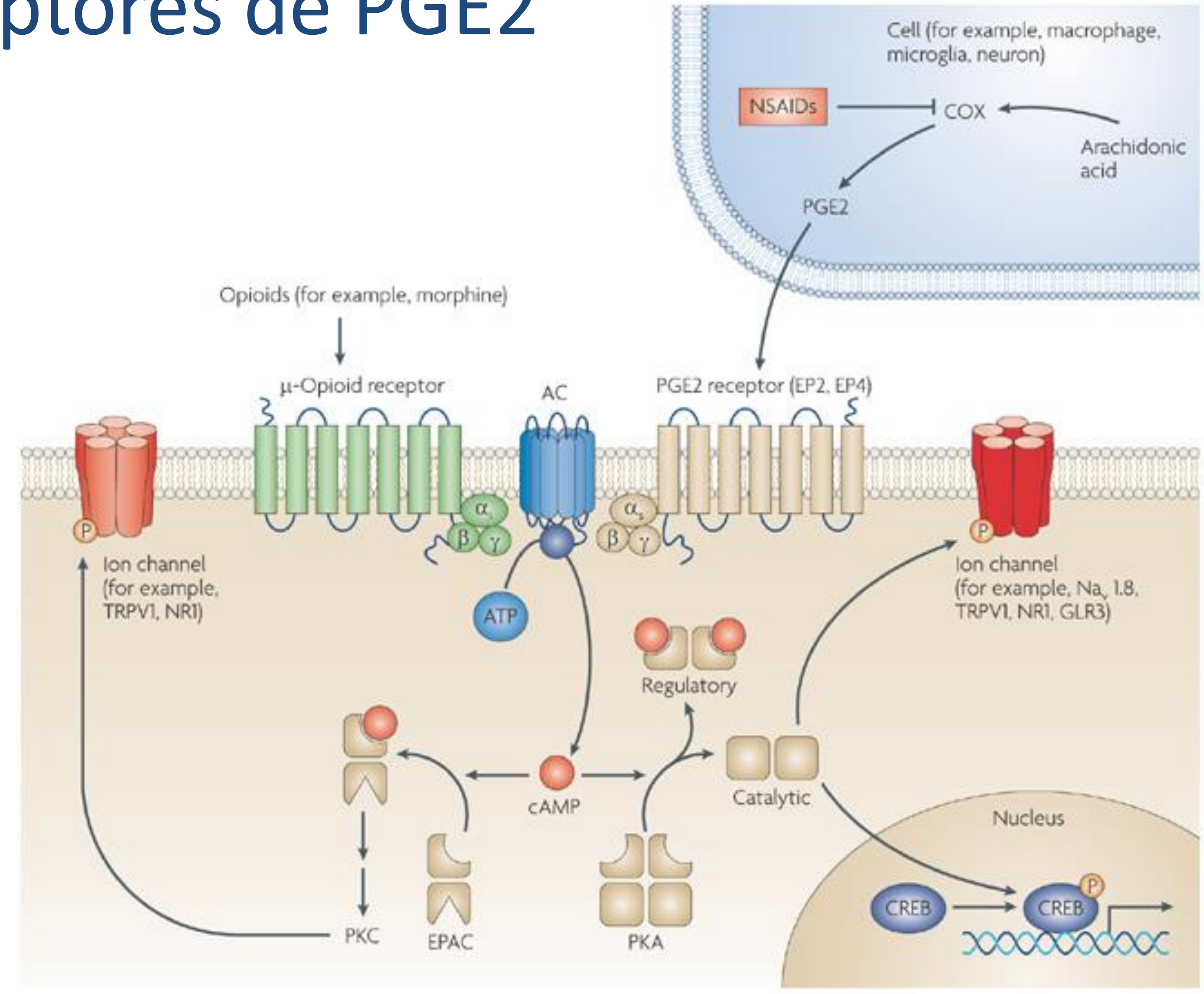
Receptores de PGE2


a
COOH
$2O_2$
Arachidonic acid
Cyclo-oxygenases
▪ COX1
▪ COX2
NSAIDs
▪ Aspirin
▪ Indomethacin
O
O
COOH
OH
PGH_2
PGE synthases
▪ Cytosolic PGES
▪ Microsomal PGES1
▪ Microsomal PGES2
O
COOH
OH
OH
PGE_2
b
O
COOH
OH
OH
PGE_2
EP1
EP2
EP3
EP4
↑Ca^{2+}
↑cAMP
↓cAMP
↑cAMP
c
EP1
EP1 agonist
ONO-DI-004
O
O
COOH
HO
OH
EP1 antagonist
ONO-8713
F_3C
O
COOH
N
CH_3
CH_3
O
S
O
O
EP2
EP2 agonist
AE1-259
Cl
COOH
HO
OH
EP2 agonist
ONO-8815
Cl
COOH
HO
OH
EP3
EP3 agonist
ONO-AE-248
O
COOH
MeO
OMe
EP4
EP4 agonist
ONO-AE1-329
O
S
S
COOH
HO
OH
OMe
EP4 agonist
ONO-4819
O
S
COOMe
HO
OH
OMe
EP4 antagonist
ONO-AE3-208
CO_2H
O
F
NC
N
H

Alta afinidade


EP2
PGE2
EP4
PGE2
EP3
PGE2
EP1
PGE2
β
γ
Gαs
Adenylate cyclase
β
γ
PO4
Gαs
GRKs
β-Arrestin
Src
PI3Ks
Akt
β
γ
Gαi
EP3α
EP3β
EP3γ
Adenylate cyclase
Rho GTPase
β
γ
Gαq
PLC
PIP3
DAG+IP3
Ca2+
ATP
cAMP
PKA
R R
PKA C
R R
PKA C
ATP
cAMP
PKA C
NF-κB
CREB
Transcription of appropriate genes

Receptores de PGE2


Cell (for example, macrophage, microglia, neuron)
NSAIDs
COX
Arachidonic acid
PGE2
Opioids (for example, morphine)
μ-Opioid receptor
AC
PGE2 receptor (EP2, EP4)
α
β
γ
α_s
β
γ
P
Ion channel (for example, TRPV1, NR1)
ATP
Regulatory
cAMP
Catalytic
P
Ion channel (for example, Na_v 1.8, TRPV1, NR1, GLR3)
Nucleus
CREB
CREB
P
PKC
EPAC
PKA

Nature Reviews | Drug Discovery

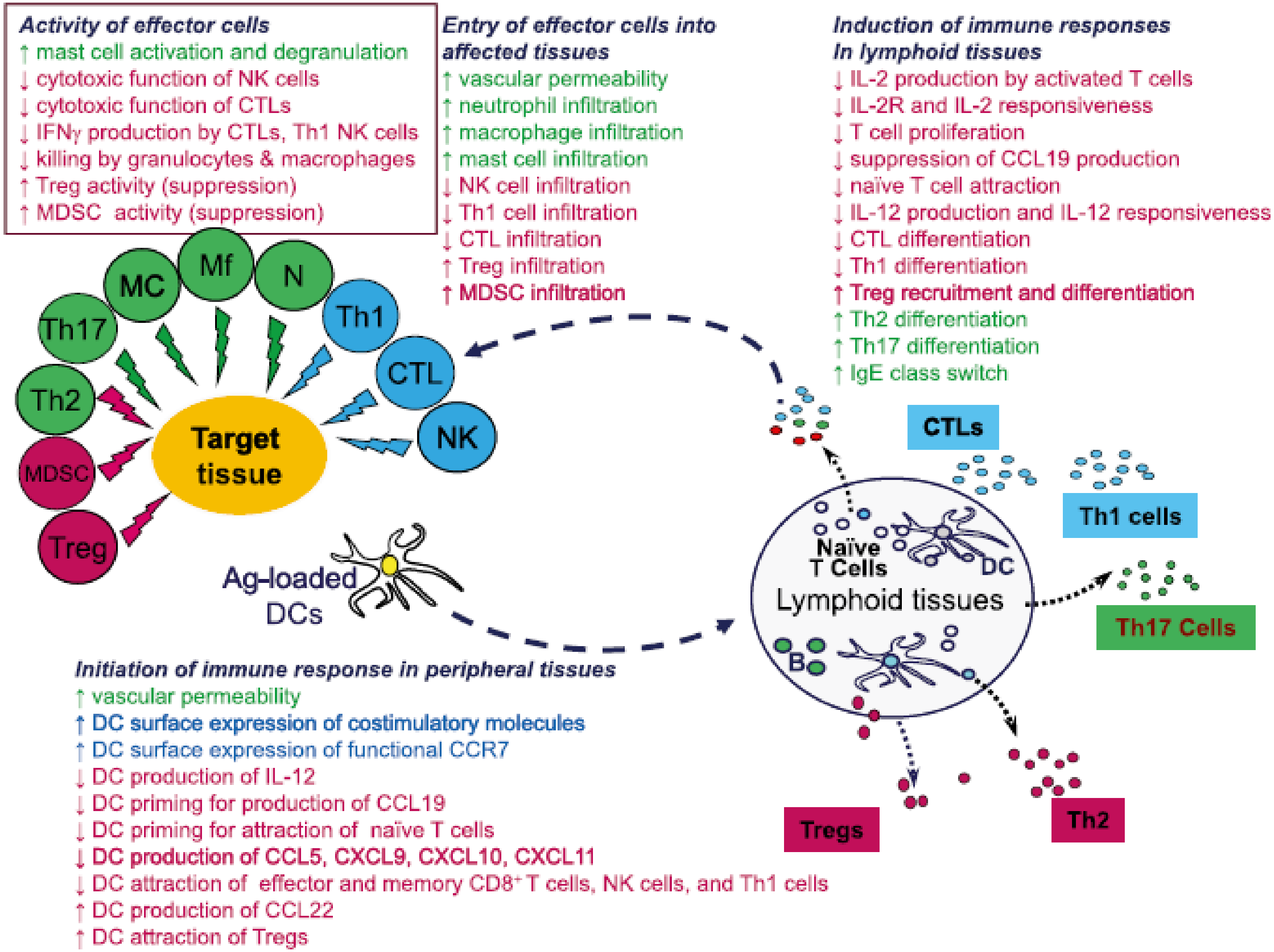
Brief Reviews

THE JOURNAL OF IMMUNOLOGY

Regulation of Immune Responses by Prostaglandin E_2

Pawel Kalinski

Mediadores Lipídicos - imunomodulação



Activity of effector cells

- ↑ mast cell activation and degranulation
- ↓ cytotoxic function of NK cells
- ↓ cytotoxic function of CTLs
- ↓ IFNγ production by CTLs, Th1 NK cells
- ↓ killing by granulocytes & macrophages
- ↑ Treg activity (suppression)
- ↑ MDSC activity (suppression)

Entry of effector cells into affected tissues

- ↑ vascular permeability
- ↑ neutrophil infiltration
- ↑ macrophage infiltration
- ↑ mast cell infiltration
- ↓ NK cell infiltration
- ↓ Th1 cell infiltration
- ↓ CTL infiltration
- ↑ Treg infiltration
- **↑ MDSC infiltration**

Induction of immune responses In lymphoid tissues

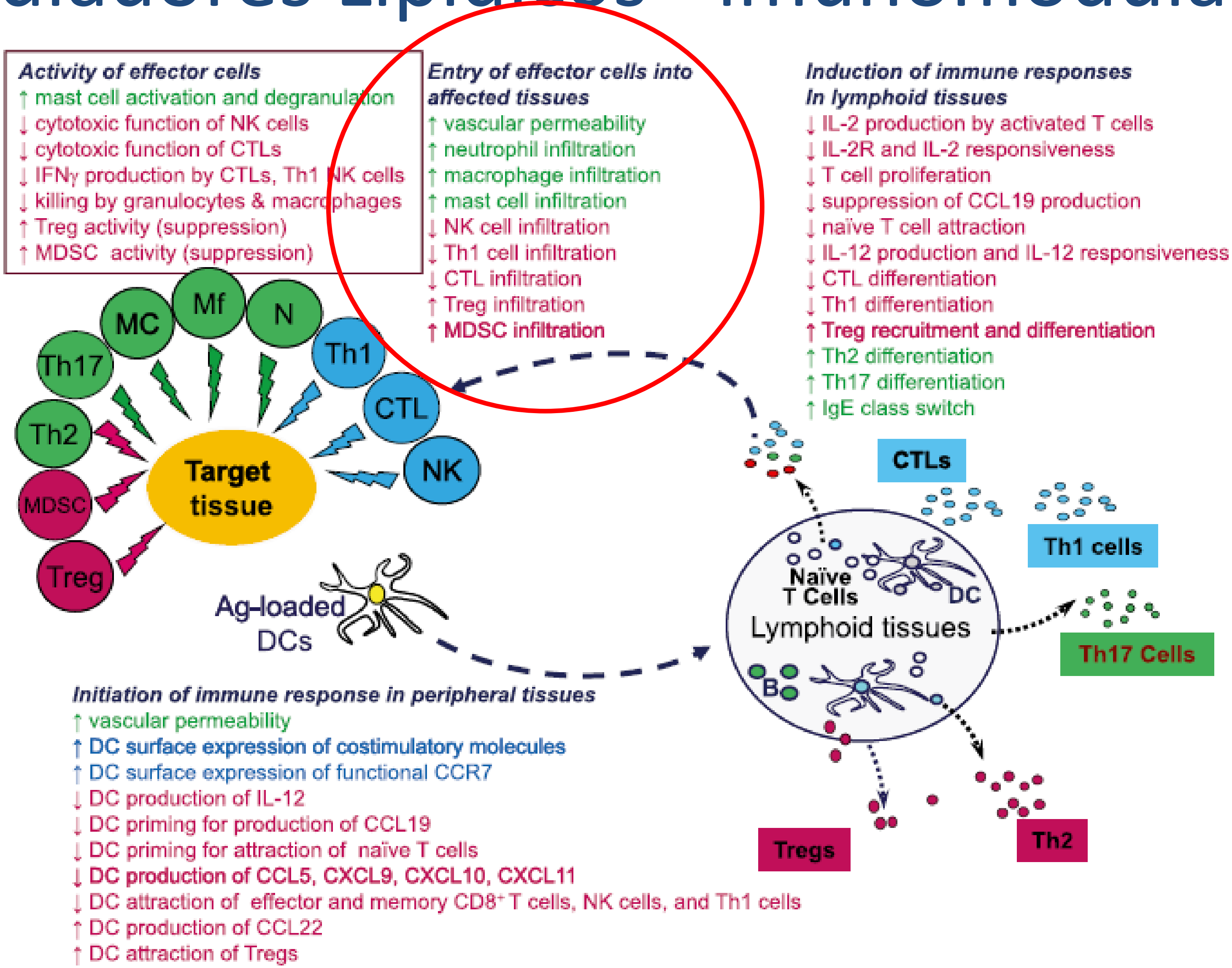
- ↓ IL-2 production by activated T cells
- ↓ IL-2R and IL-2 responsiveness
- ↓ T cell proliferation
- ↓ suppression of CCL19 production
- ↓ naïve T cell attraction
- ↓ IL-12 production and IL-12 responsiveness
- ↓ CTL differentiation
- ↓ Th1 differentiation
- **↑ Treg recruitment and differentiation**
- ↑ Th2 differentiation
- ↑ Th17 differentiation
- ↑ IgE class switch

Initiation of immune response in peripheral tissues

- ↑ vascular permeability
- **↑ DC surface expression of costimulatory molecules**
- ↑ DC surface expression of functional CCR7
- ↓ DC production of IL-12
- ↓ DC priming for production of CCL19
- ↓ DC priming for attraction of naïve T cells
- **↓ DC production of CCL5, CXCL9, CXCL10, CXCL11**
- ↓ DC attraction of effector and memory CD8$^+$ T cells, NK cells, and Th1 cells
- ↑ DC production of CCL22
- ↑ DC attraction of Tregs

Azul: relevante para patógenos intracelulares e cancer
Verde: relevante para patógenos extracelulares

Mediadores Lipídicos - imunomodulação



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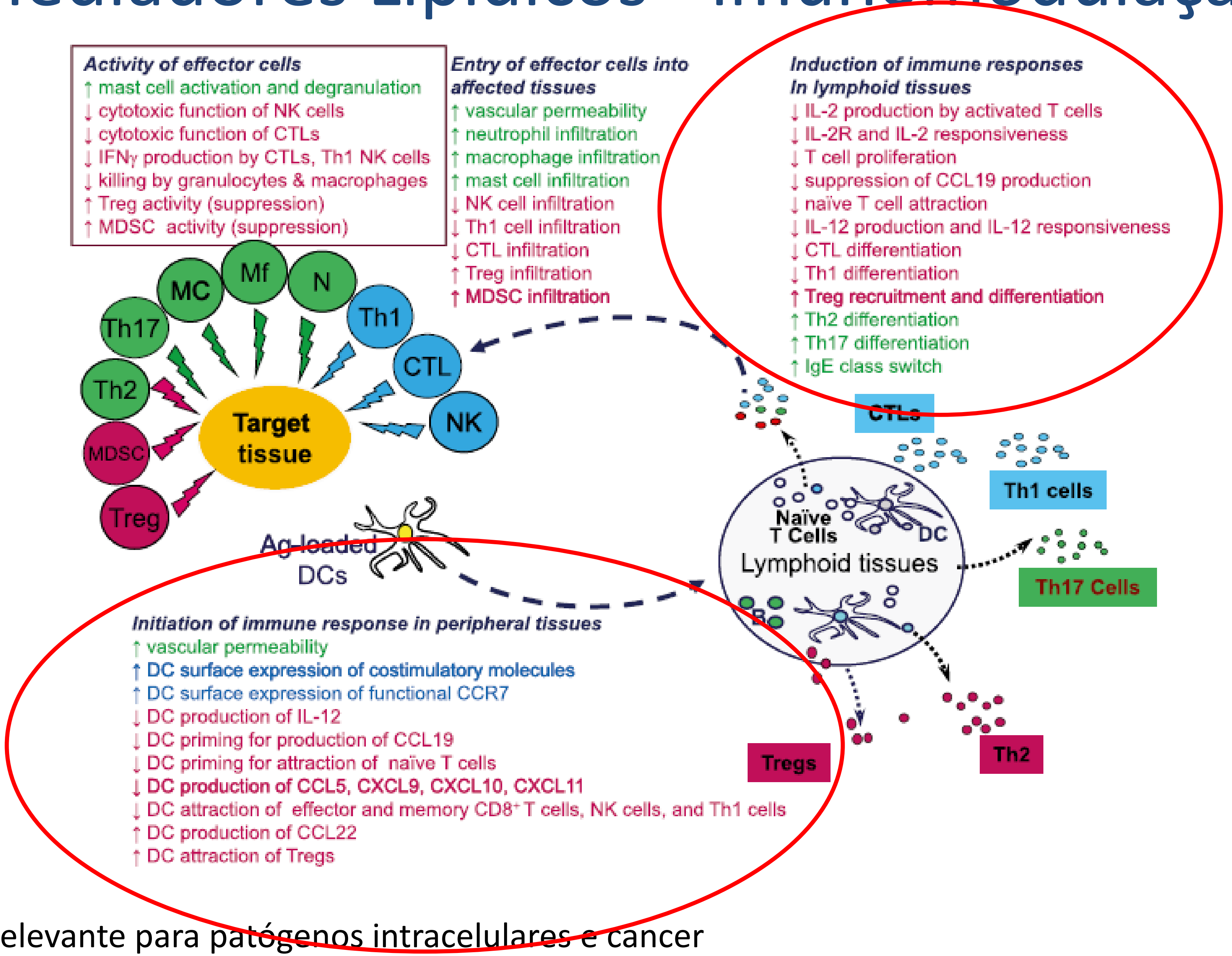
Verde: relevante para patógenos extracelulares

Mediadores Lipídicos - imunomodulação



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Azul: relevante para patógenos intracelulares e cancer

Verde: relevante para patógenos extracelulares

Journal of Neuroimmunology 238 (2011) 34–43

Contents lists available at ScienceDirect

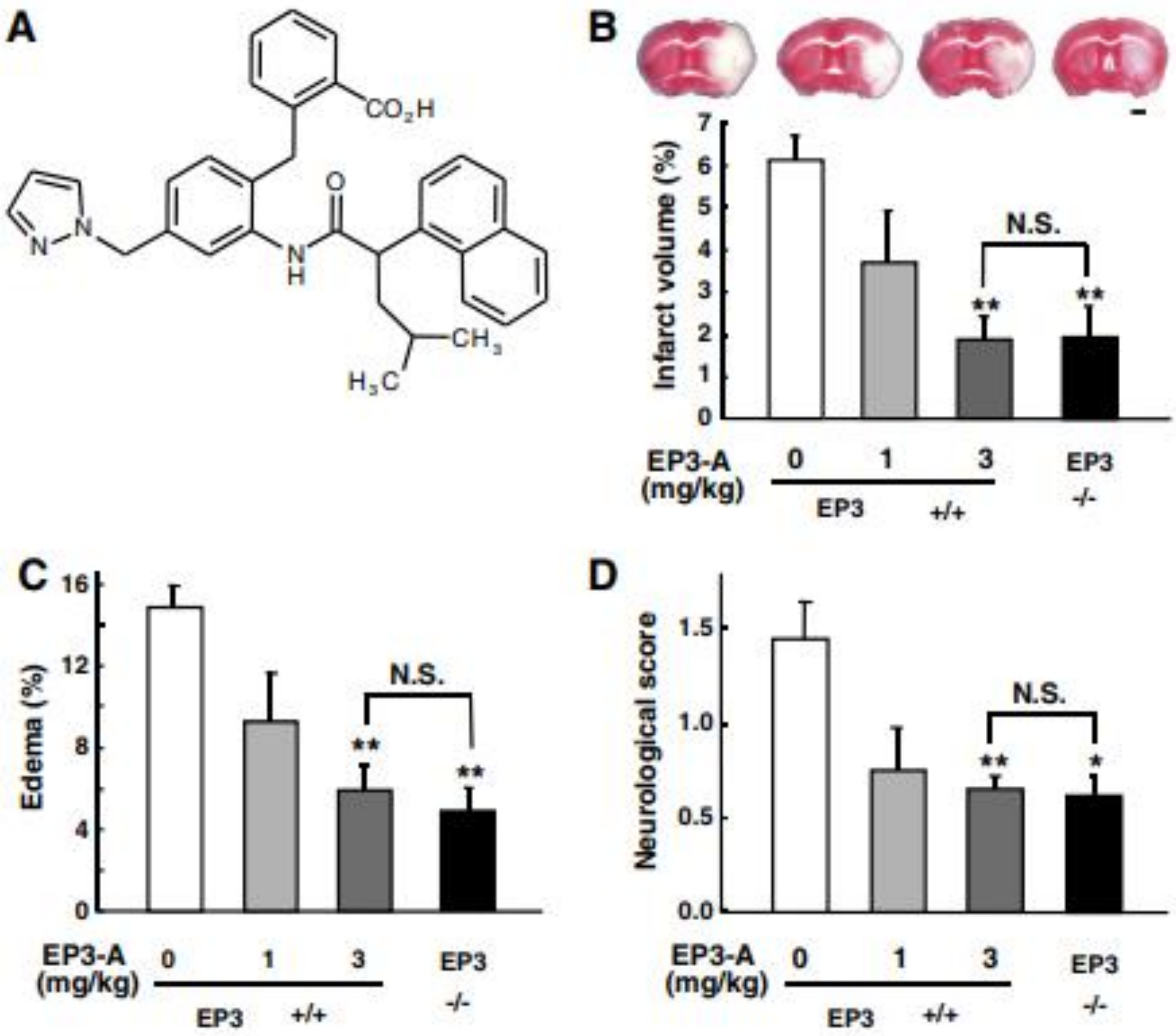
Journal of Neuroimmunology

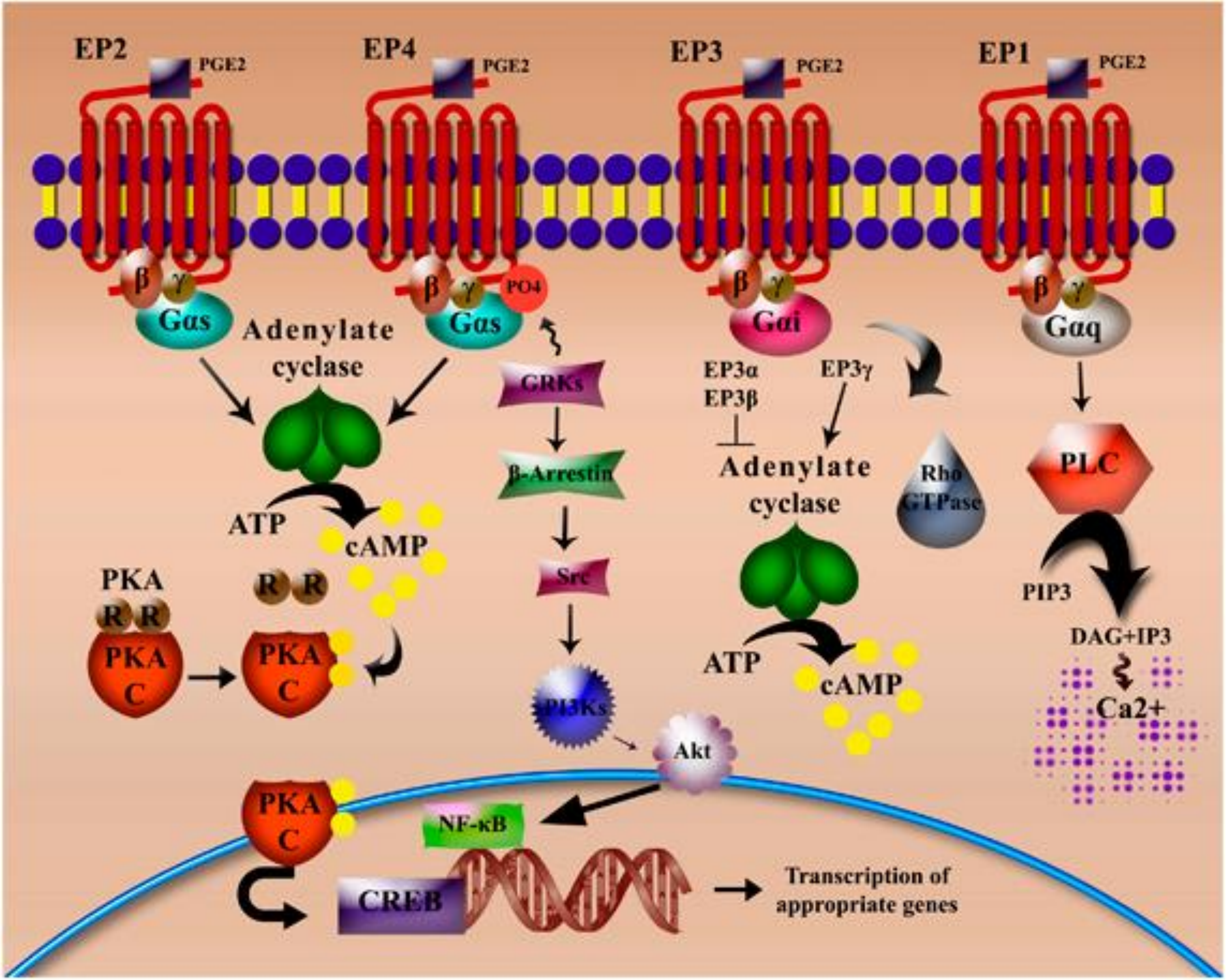
journal homepage: www.elsevier.com/locate/jneuroim

Inhibition of prostaglandin E_2 EP3 receptors improves stroke injury *via* anti-inflammatory and anti-apoptotic mechanisms

Yuri Ikeda-Matsuo [a,*], Hayato Tanji [a], Shuh Narumiya [b], Yasuharu Sasaki [a]

[a] *Laboratory of Pharmacology, School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan*
[b] *Department of Pharmacology, Kyoto University Faculty of Medicine, Kyoto, Japan*


A
CO₂H
O
N
N
N
H
CH₃
H₃C
B
Infarct volume (%)
0
1
2
3
4
5
6
7
N.S.
**
**
EP3-A (mg/kg)
0
1
3
EP3 +/+
EP3 -/-
C
Edema (%)
0
4
8
12
16
N.S.
**
**
EP3-A (mg/kg)
0
1
3
EP3 +/+
EP3 -/-
D
Neurological score
0.0
0.5
1.0
1.5
N.S.
**
*
EP3-A (mg/kg)
0
1
3
EP3 +/+
EP3 -/-


EP2
PGE2
EP4
PGE2
EP3
PGE2
EP1
PGE2
β
γ
Gαs
β
γ
PO4
Gαs
β
γ
Gαi
β
γ
Gαq
Adenylate cyclase
GRKs
β-Arrestin
Src
PI3Ks
Akt
ATP
cAMP
PKA
R R
PKA C
R R
PKA C
EP3α
EP3β
EP3γ
Adenylate cyclase
Rho GTPase
ATP
cAMP
PLC
PIP3
DAG+IP3
Ca2+
PKA C
NF-κB
CREB
Transcription of appropriate genes

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JPET 309:1213–1220, 2004

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62646/1146989
Printed in U.S.A.

E-Prostanoid (EP)2/EP4 Receptor-Dependent Maturation of Human Monocyte-Derived Dendritic Cells and Induction of Helper T2 Polarization

Shinichiro Kubo, Hideo Kohka Takahashi, Masao Takei, Hiromi Iwagaki, Tadashi Yoshino, Noriaki Tanaka, Shuji Mori, and Masahiro Nishibori

Departments of Pharmacology (S.K., H.K.T., S.M., M.N.), Tumour Biology (S.K., H.K.T., H.I., N.T.), and Pathology (T.Y.), Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan; and Forshungazentrum Borstel (M.T.), Borstel, Germany

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Molecular Immunology 54 (2013) 284–295

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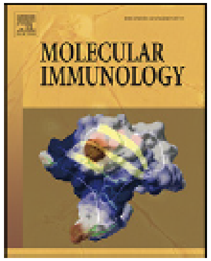
journal homepage: www.elsevier.com/locate/molimm



PGE_2 differentially regulates monocyte-derived dendritic cell cytokine responses depending on receptor usage (EP_2/EP_4)☆

Neil J. Poloso[a,*], Paula Urquhart[b], Anna Nicolaou[b], Jenny Wang[a], David F. Woodward[a]

[a] 2525 DuPont Dr, RD3-2B, Department Biological Sciences, Allergan Inc., Irvine, CA 92612, USA
[b] Bradford School of Pharmacy, School of Life Sciences, University of Bradford, Bradford BD7 1PD, UK

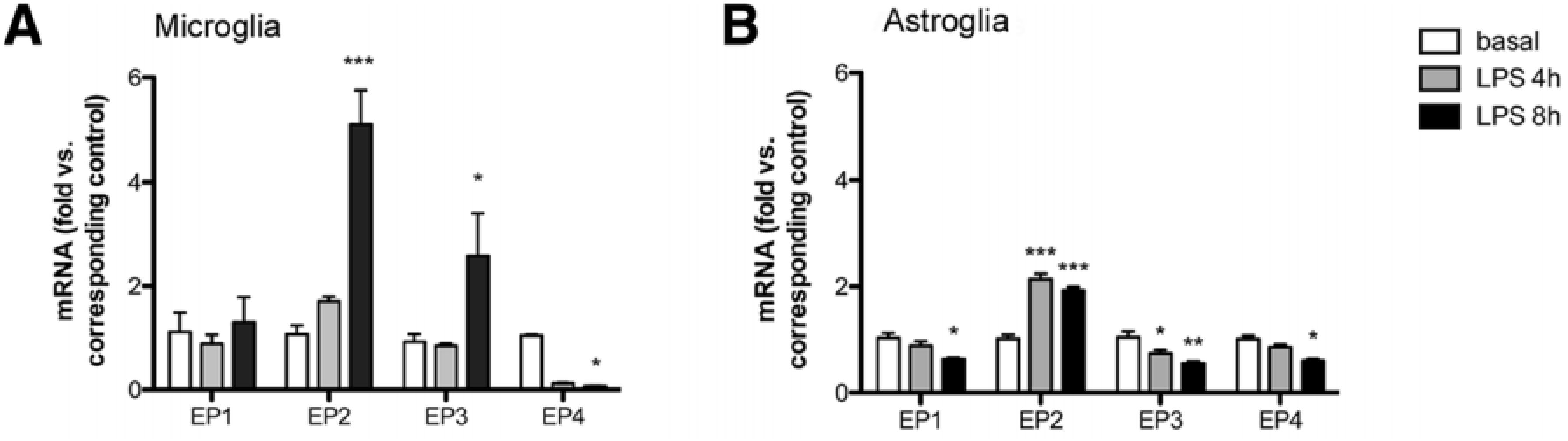
Bonfill-Teixidor *et al. Journal of Neuroinflammation* (2017) 14:3
DOI 10.1186/s12974-016-0780-7

Journal of Neuroinflammation

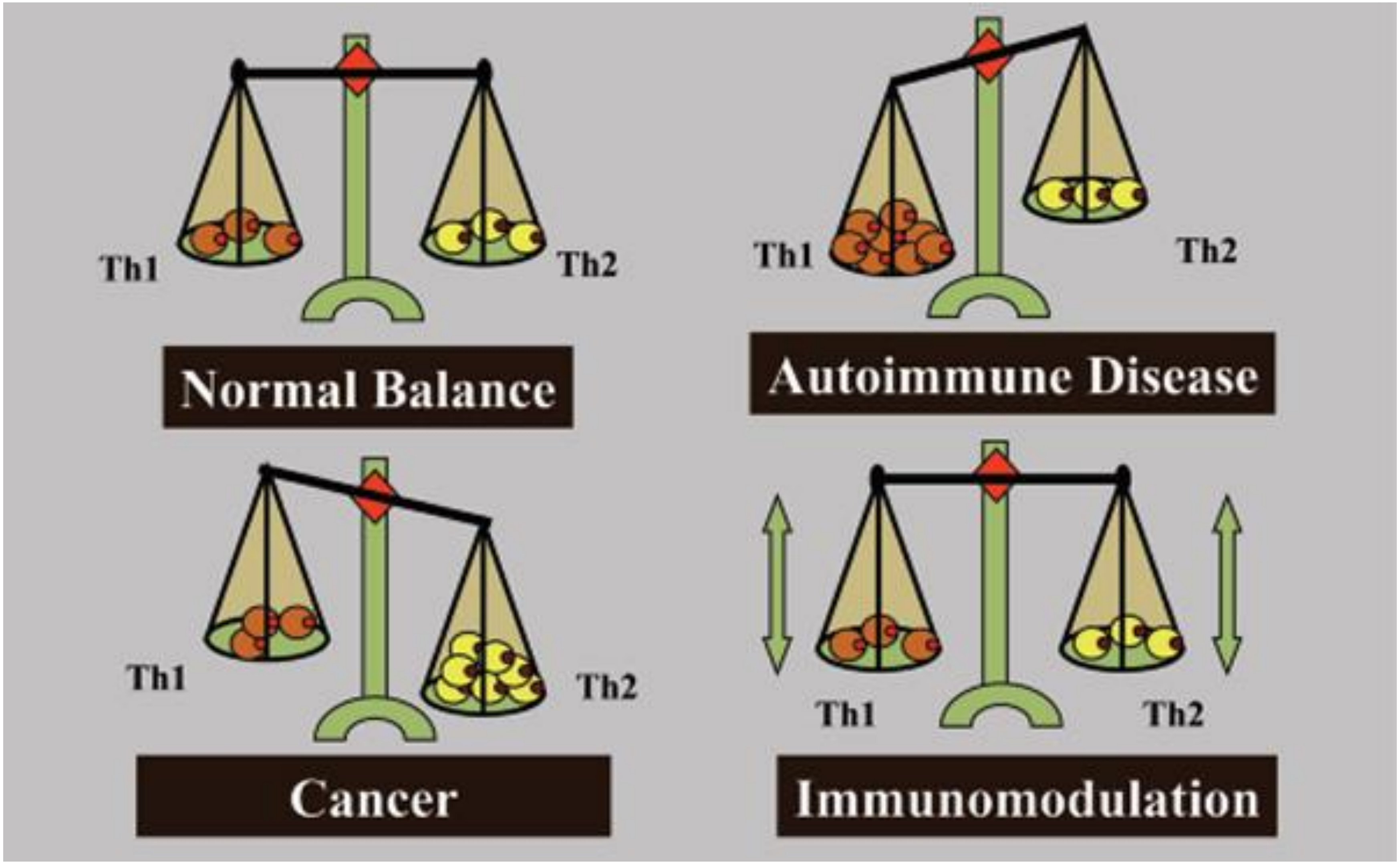
RESEARCH **Open Access**

Differential expression of E-type prostanoid receptors 2 and 4 in microglia stimulated with lipopolysaccharide

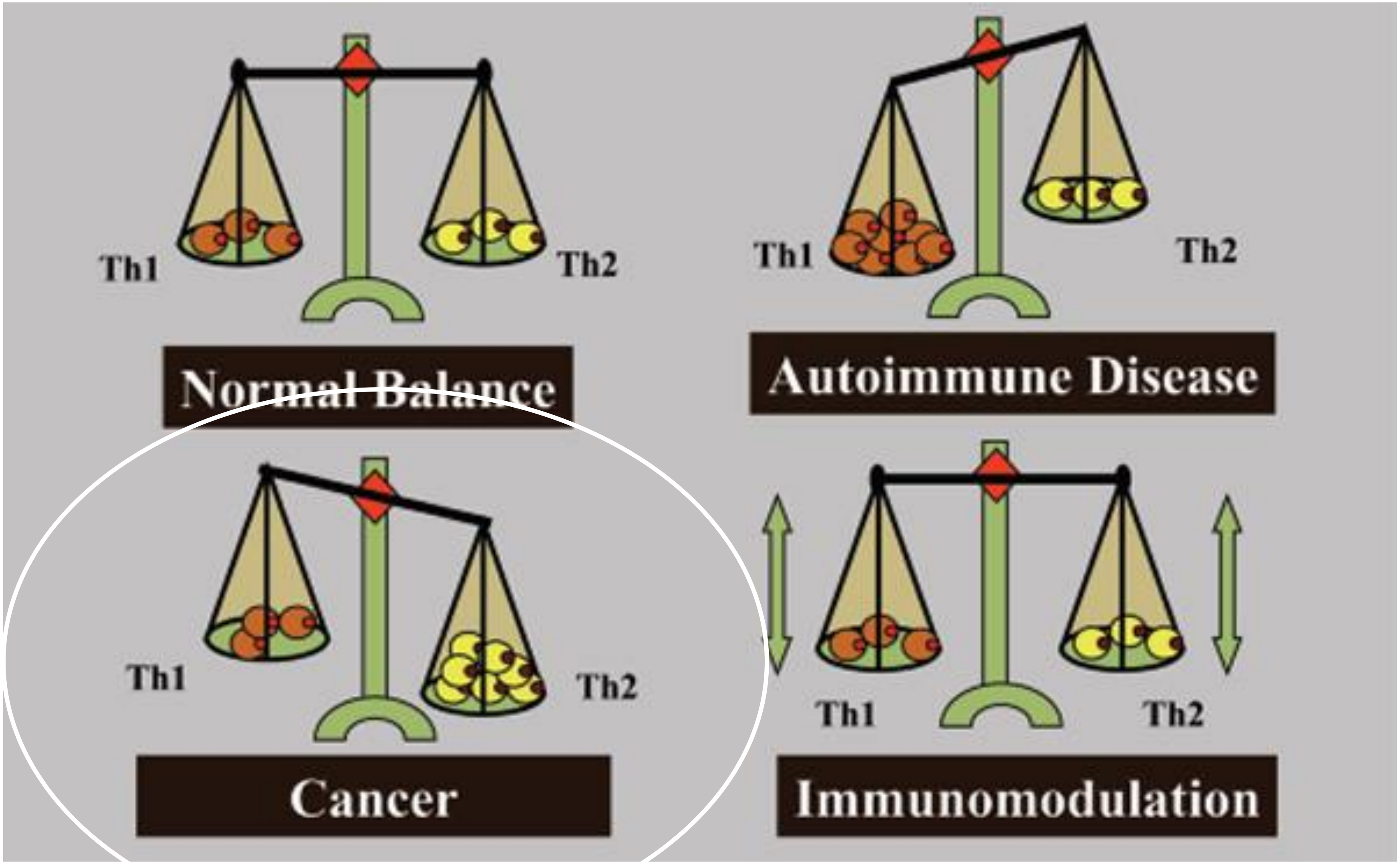
Ester Bonfill-Teixidor[1,2], Amaia Otxoa-de-Amezaga[1,2], Miriam Font-Nieves[1], M. Glòria Sans-Fons[2] and Anna M. Planas[1,2,3*]



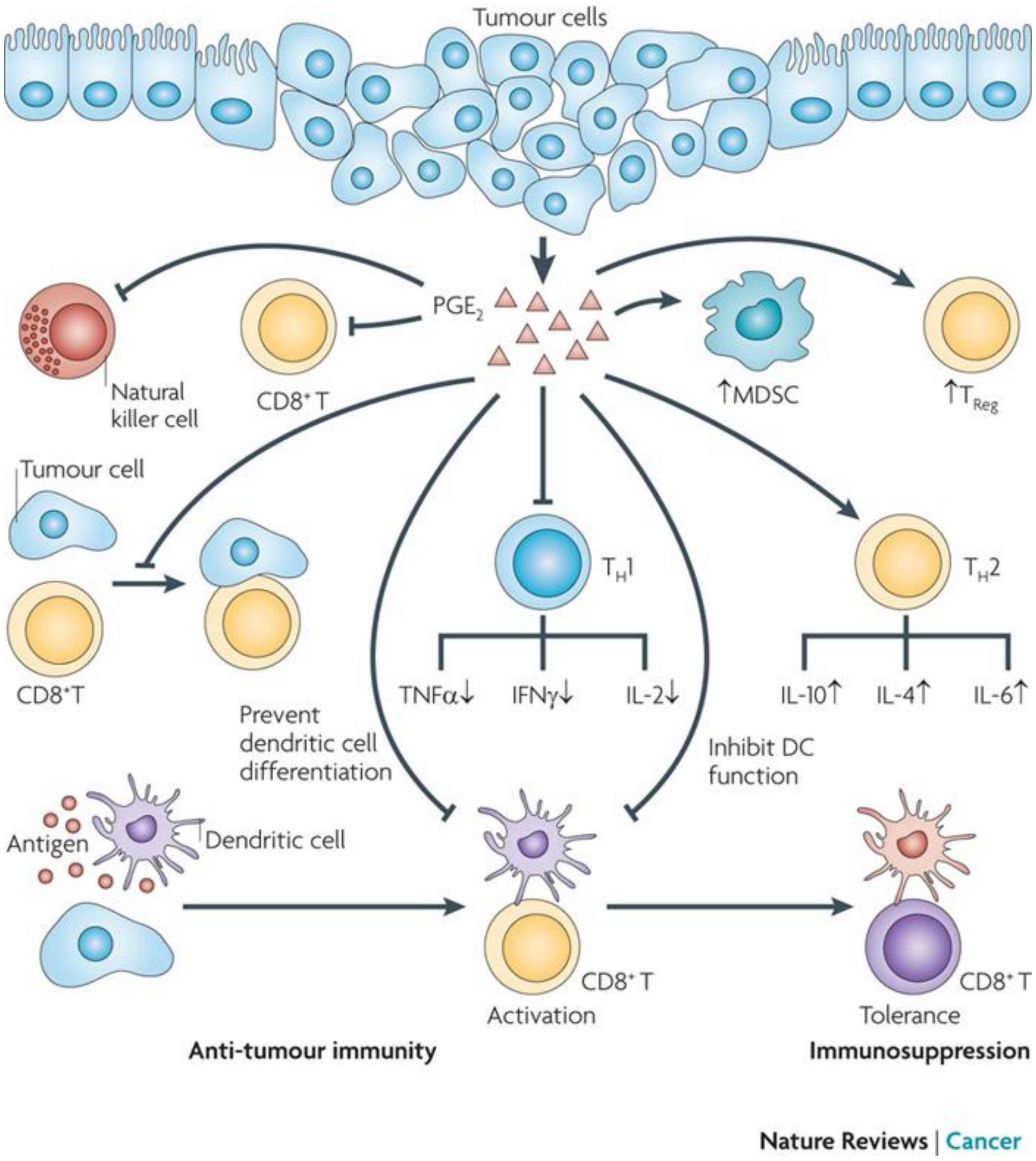
Balanço Th1/Th2


Th1
Th2
Normal Balance
Th1
Th2
Autoimmune Disease
Th1
Th2
Cancer
Th1
Th2
Immunomodulation

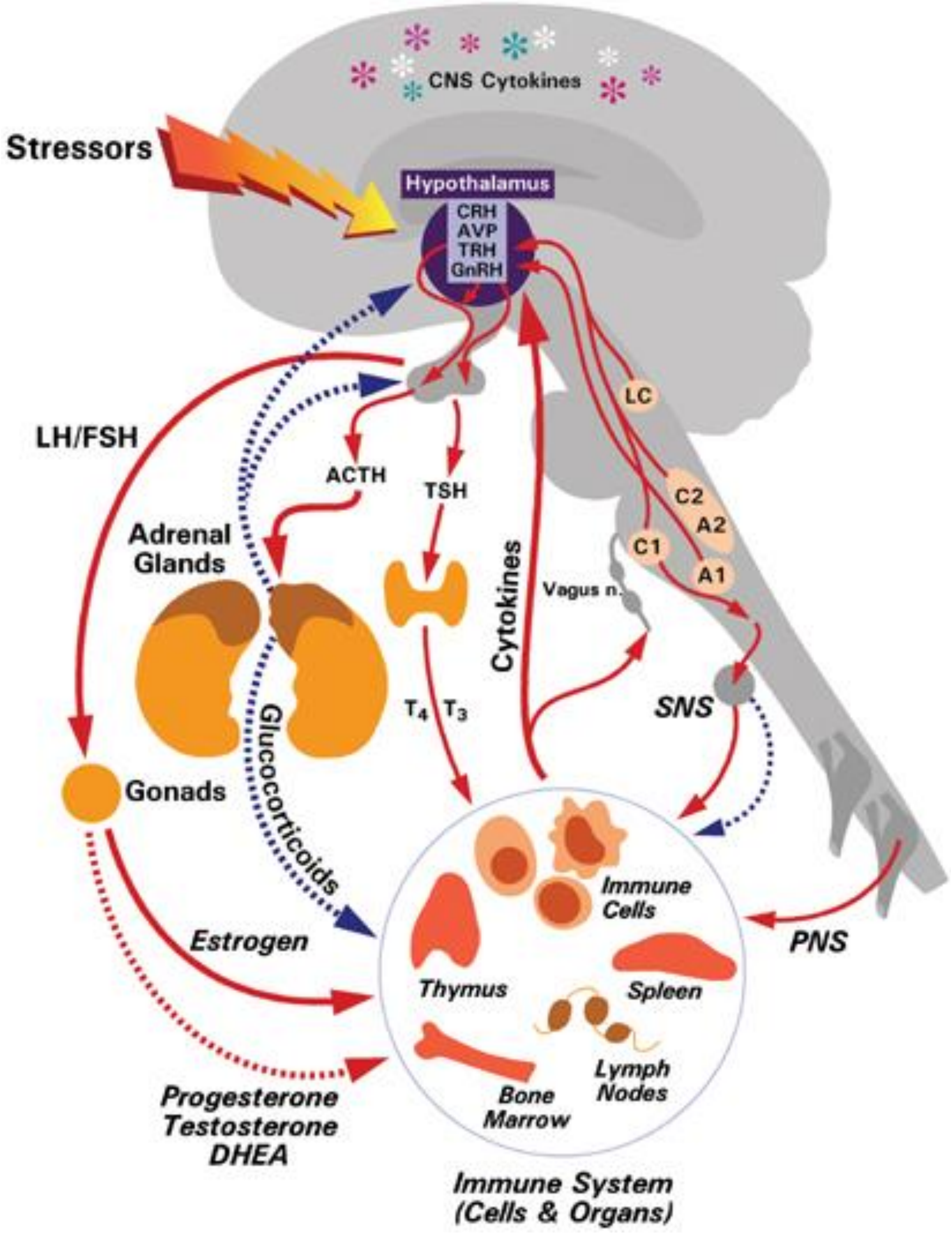
Balanço Th1/Th2


Th1
Th2
Normal Balance
Th1
Th2
Autoimmune Disease
Th1
Th2
Cancer
Th1
Th2
Immunomodulation

Mediadores Lipídicos - imunomodulação


Tumour cells
PGE$_2$
Natural killer cell
CD8$^+$ T
↑MDSC
↑T$_{Reg}$
Tumour cell
CD8$^+$T
T$_H$1
T$_H$2
TNFα↓
IFNγ↓
IL-2↓
IL-10↑
IL-4↑
IL-6↑
Prevent dendritic cell differentiation
Inhibit DC function
Antigen
Dendritic cell
CD8$^+$ T
Activation
CD8$^+$ T
Tolerance
Anti-tumour immunity
Immunosuppression
Nature Reviews | Cancer

Mediadores Lipídicos - Neuroimunomodulação


CNS Cytokines
Stressors
Hypothalamus
CRH
AVP
TRH
GnRH
LH/FSH
ACTH
TSH
Adrenal Glands
Cytokines
LC
C2
A2
C1
A1
Vagus n.
SNS
Gonads
Glucocorticoids
T_4 T_3
Immune Cells
Thymus
Spleen
Estrogen
PNS
Lymph Nodes
Bone Marrow
Progesterone
Testosterone
DHEA
Immune System
(Cells & Organs)

Mediadores Lipídicos - Ações

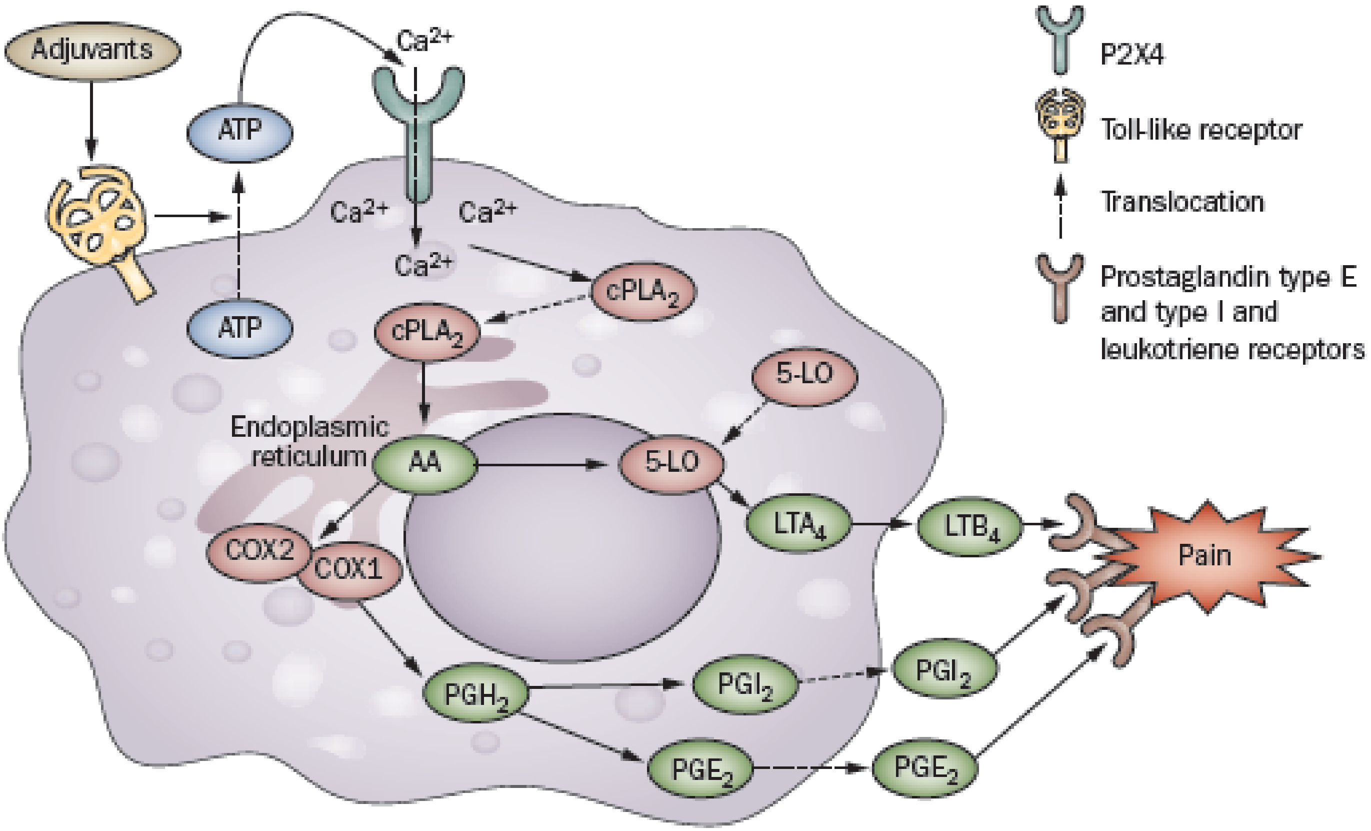
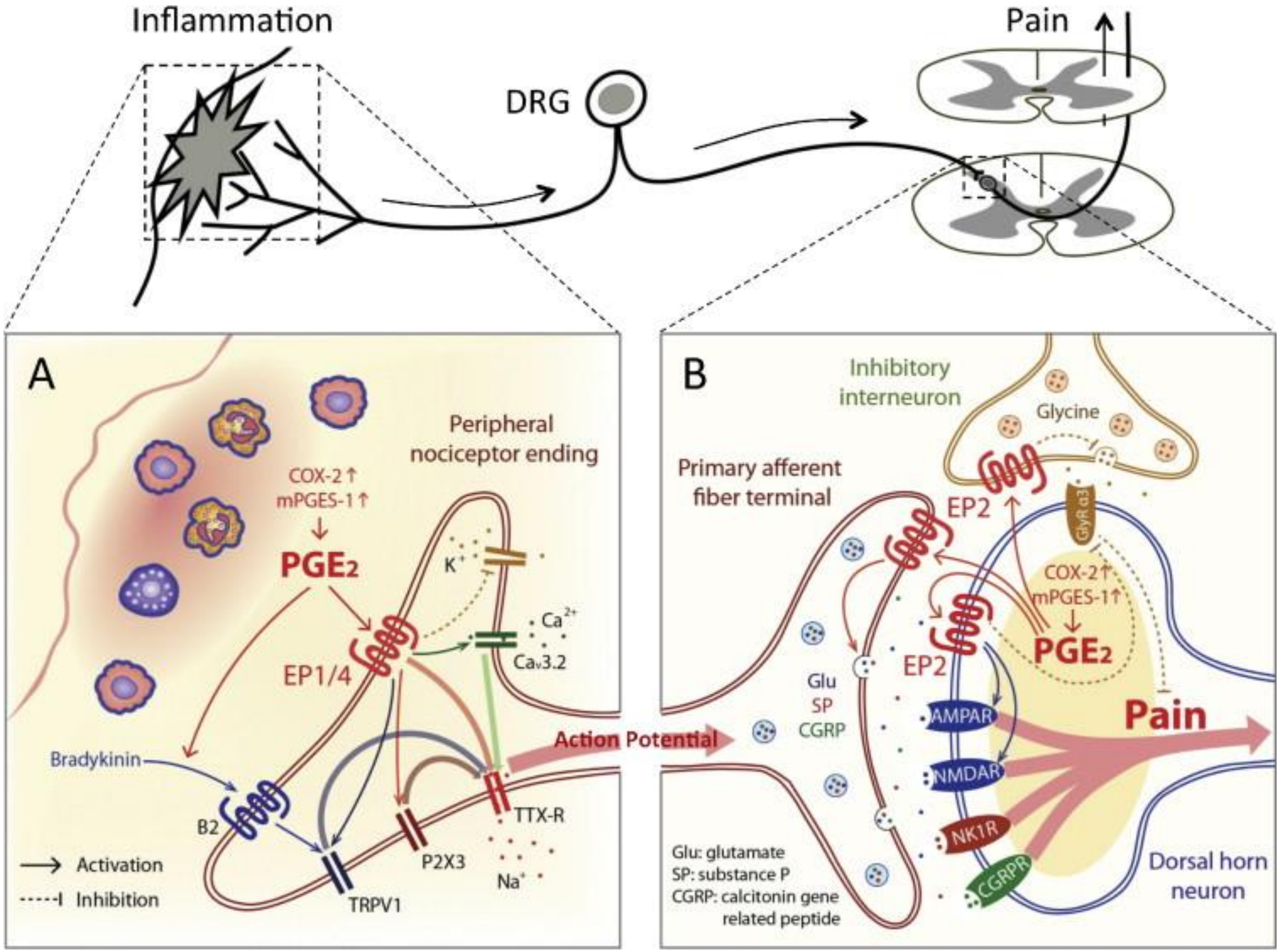
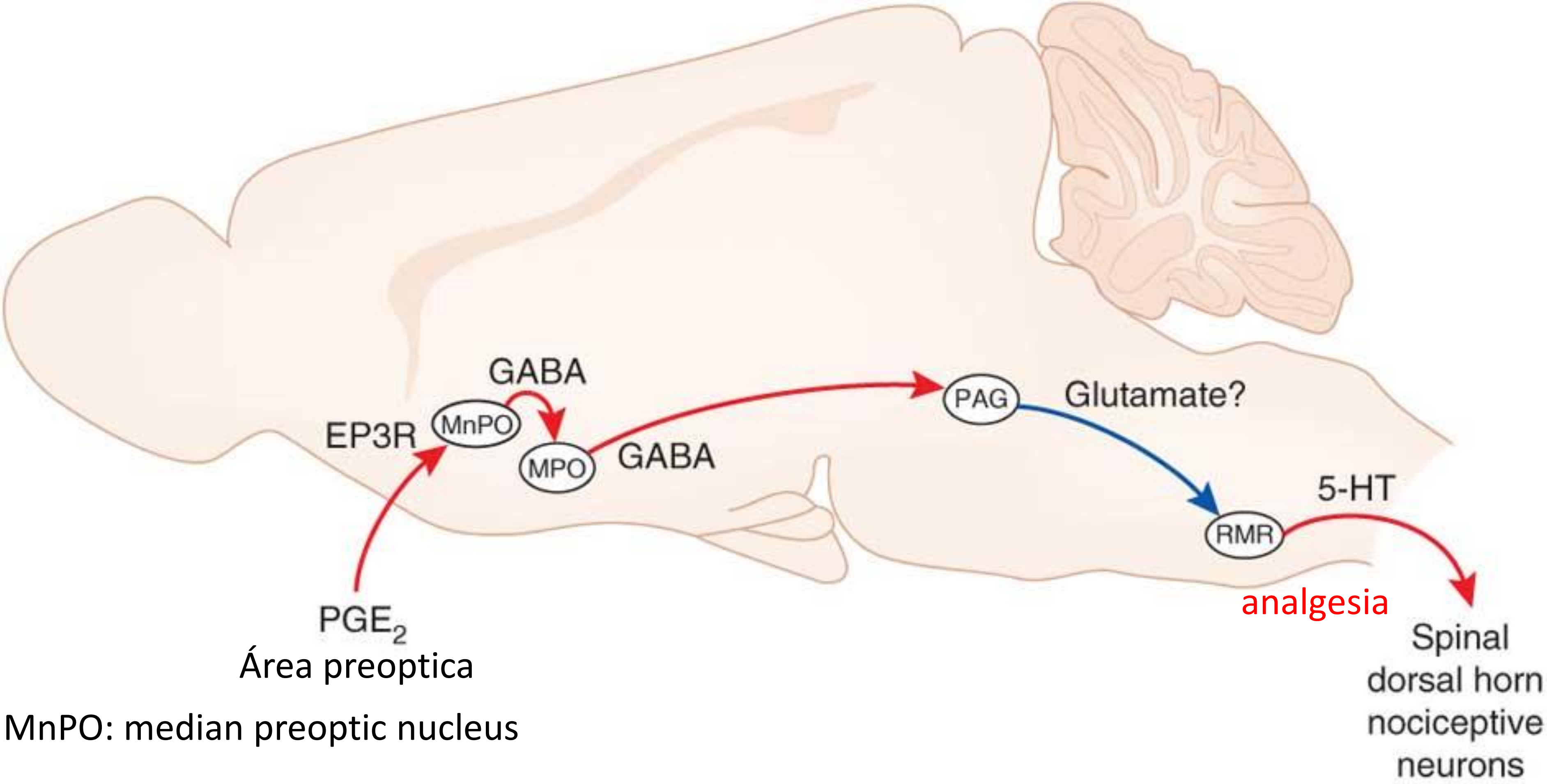

Adjuvants
ATP
Ca2+
Ca2+
Ca2+
Ca2+
ATP
cPLA2
cPLA2
5-LO
Endoplasmic reticulum
AA
5-LO
COX2
COX1
LTA4
LTB4
Pain
PGH2
PGI2
PGI2
PGE2
PGE2
P2X4
Toll-like receptor
Translocation
Prostaglandin type E and type I and leukotriene receptors

Figure 1 | The proposed P2X4 pathway to pain. ATP, released following adjuvant stimulation of Toll-like receptors, opens the P2X4 receptor, in turn causing calcium influx. A cascade of events ensues, including calcium-dependent translocations of $cPLA_2$ and 5-LO to the nucleus and endoplasmic reticulum. $cPLA_2$ liberates AA, the substrate for COX1, COX2 and 5-LO. These enzymes catalyze the formation of PGH_2 and LTA_4, respectively, which are further metabolized to terminal prostaglandins and leukotrienes. PGE_2, PGI_2 and LTB_4 evoke pain responses via their respective receptors. Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase A_2; 5-LO, 5-lipoxygenase; LTA_4, leukotriene A_4; LTB_4, leukotriene B_4; PGE_2, prostaglandin E_2; PGI_2, prostacyclin; PGH_2, prostaglandin H_2.

Mediadores Lipídicos - Ações


Inflammation
DRG
Pain
A
Peripheral nociceptor ending
COX-2 ↑
mPGES-1 ↑
PGE2
K+
Ca2+
CaV3.2
EP1/4
Bradykinin
B2
TRPV1
P2X3
TTX-R
Na+
Activation
Inhibition
Action Potential
B
Inhibitory interneuron
Glycine
Primary afferent fiber terminal
EP2
GlyR α3
COX-2↑
mPGES-1↑
PGE2
EP2
Glu
SP
CGRP
AMPAR
NMDAR
NK1R
CGRPR
Pain
Dorsal horn neuron
Glu: glutamate
SP: substance P
CGRP: calcitonin gene related peptide

Papel das PGs- DOR


GABA
EP3R
MnPO
MPO
GABA
PAG
Glutamate?
5-HT
RMR
analgesia
PGE_2
Área preoptica
Spinal dorsal horn nociceptive neurons

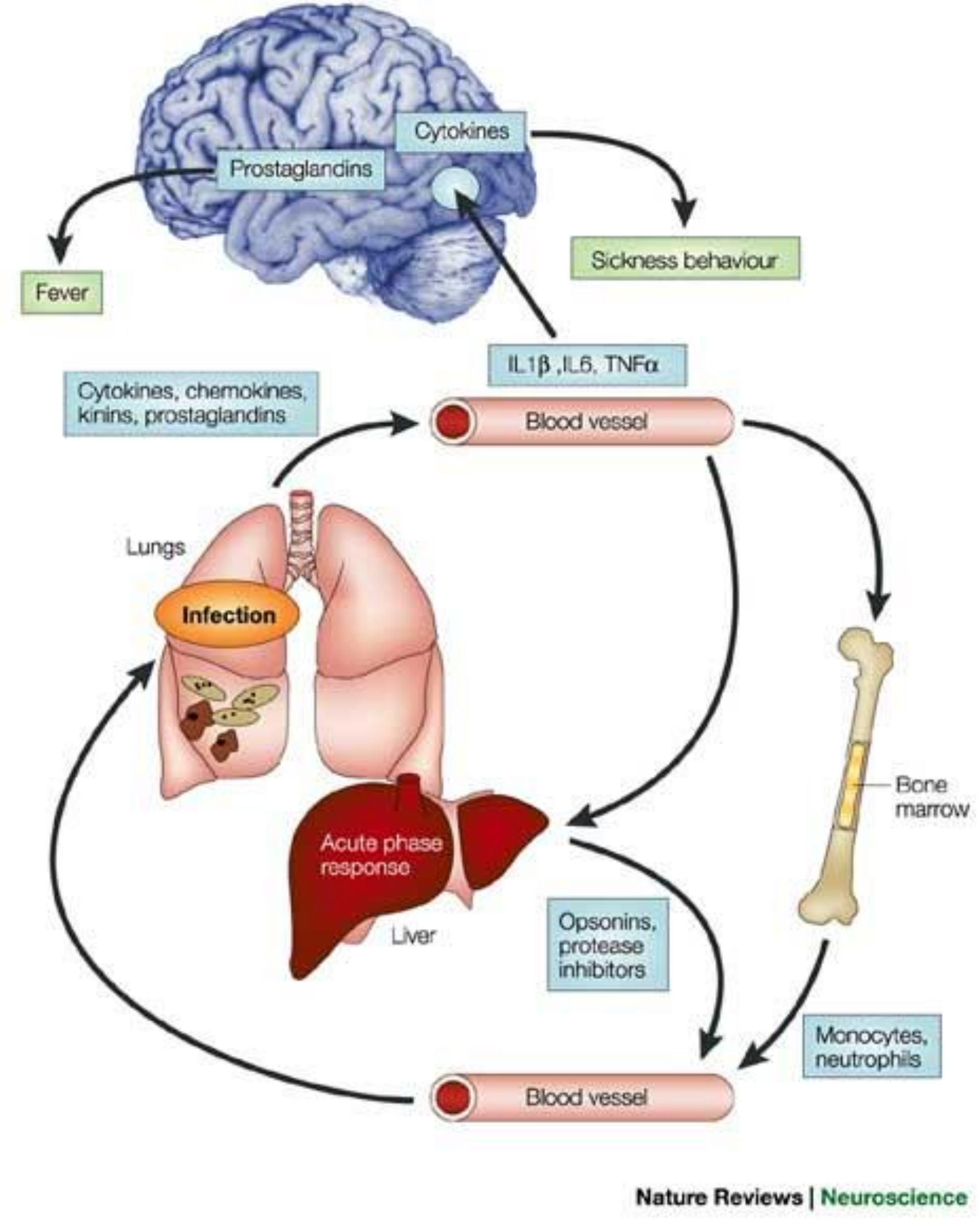
MnPO: median preoptic nucleus

PGE2 inibe MnPO levando a desinibição de vias descendentes inibitórias da MPO (medial preoptic area) para o sistema antinociceptivo.

PAG : periaqueductal gray matter

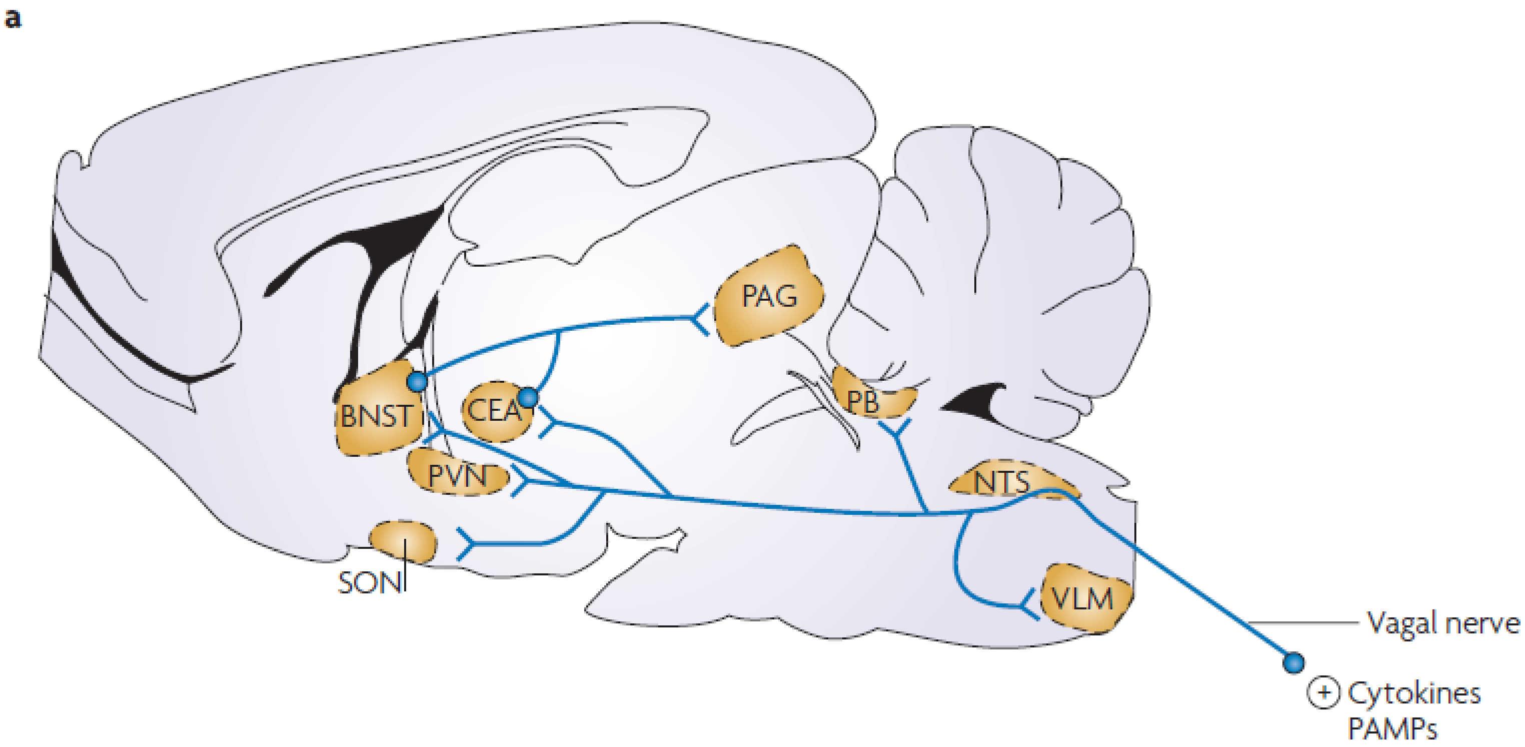
RMR: rostral medullary raphe

Papel das PGs na neuroimunomodulação


Cytokines
Prostaglandins
Fever
Sickness behaviour
IL1β ,IL6, TNFα
Cytokines, chemokines, kinins, prostaglandins
Blood vessel
Lungs
Infection
Acute phase response
Liver
Bone marrow
Opsonins, protease inhibitors
Monocytes, neutrophils
Blood vessel

Nature Reviews | Neuroscience

Reflexo vagal


a
PAG
BNST
CEA
PB
PVN
NTS
SON
VLM
Vagal nerve
+ Cytokines
PAMPs

Via aferente

Reflexo vagal

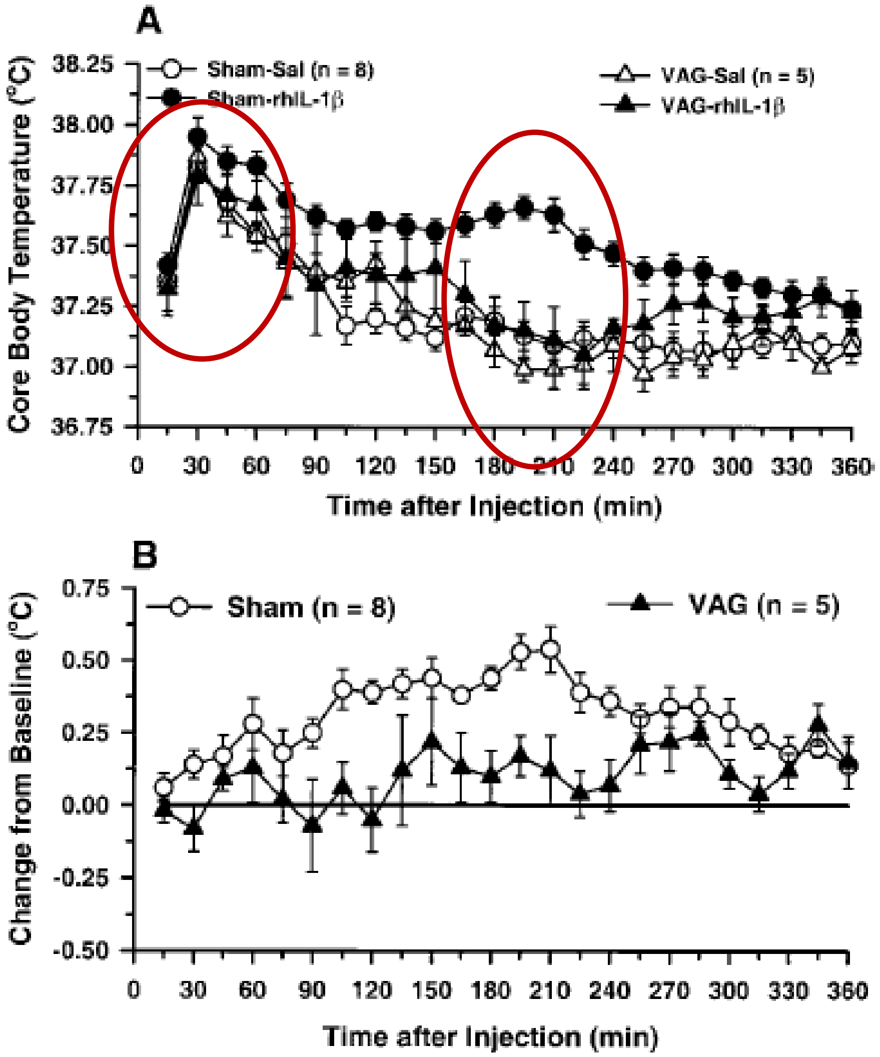


Fig. 1. *A*: mean core body temperature for sham surgery (Sham) and vagotomized (Vag) subjects injected at *time 0* with saline (Sal) or 0.1 μg/kg recombinant human interleukin-1β (rh-IL-1β). *B*: the difference between core body temperature after injection with rh-IL-1β and after Sal for Sham and Vag subjects.

Efeito relativo do vago no controle do aumento da temperatura corporal induzida por administração de IL-β

Via aferente

Reflexo vagal

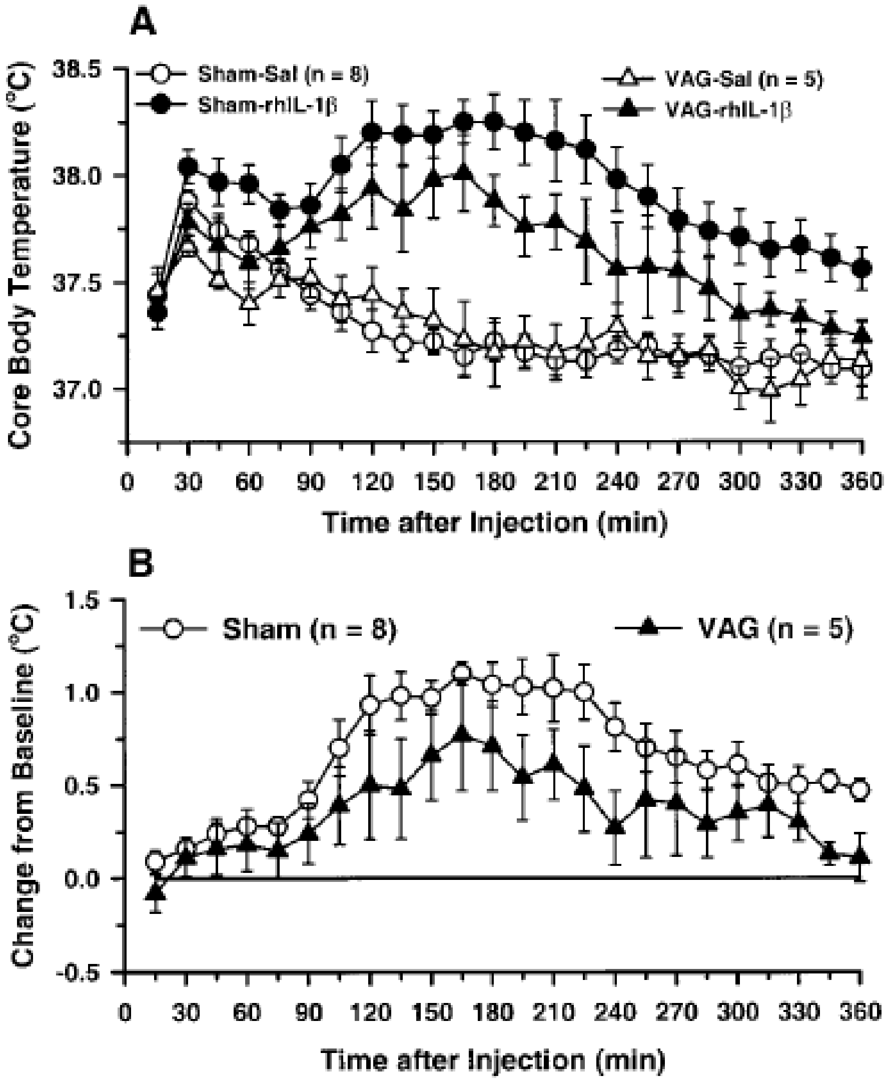


Fig. 2. *A*: mean core body temperature for Sham and Vag subjects injected at *time 0* with Sal or 0.5 µg/kg rh-IL-1β. *B*: the difference between core body temperature after injection with rh-IL-1β and after Sal for Sham and Vag subjects.

Efeito relativo do vago no controle do aumento da temperatura corporal induzida por administração de IL-β

Via aferente

Reflexo vagal

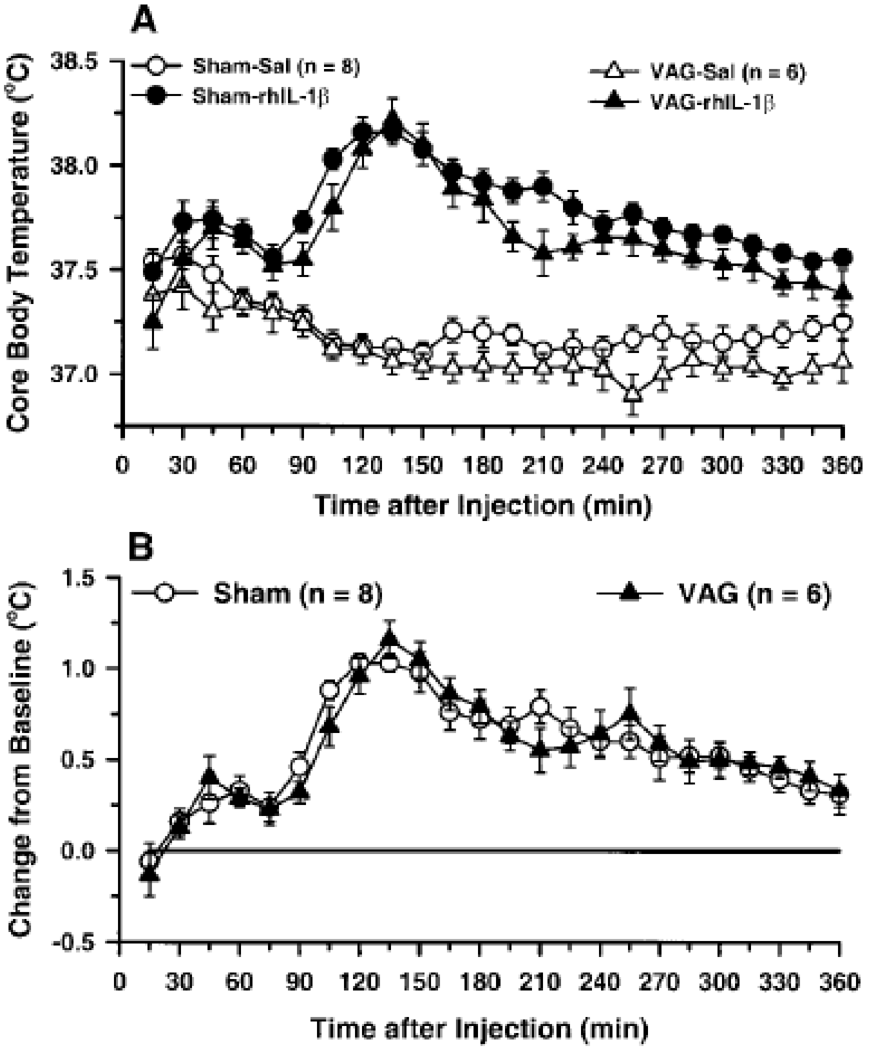


Fig. 3. *A*: mean core body temperature for Sham and Vag subjects injected at *time 0* with Sal or 1.0 μg/kg rh-IL-1β. *B*: the difference between core body temperature after injection with rh-IL-1β and after Sal for Sham and Vag subjects.

Efeito relativo do vago no controle do aumento da temperatura corporal induzida por administração de IL-β

Via aferente

THE JOURNAL OF COMPARATIVE NEUROLOGY 381:119–129 (1997)

Intravenous Lipopolysaccharide Induces Cyclooxygenase 2-Like Immunoreactivity in Rat Brain Perivascular Microglia and Meningeal Macrophages

JOEL K. ELMQUIST,[1]* CHRISTOPHER D. BREDER,[2] JONATHAN E. SHERIN,[1]
THOMAS E. SCAMMELL,[1] WILLIAM F. HICKEY,[3] DAVID DEWITT,[4]
AND CLIFFORD B. SAPER[1]
[1]Department of Neurology and Program in Neuroscience, Harvard Medical School,
Beth Israel Hospital, Boston, Massachusetts 02115
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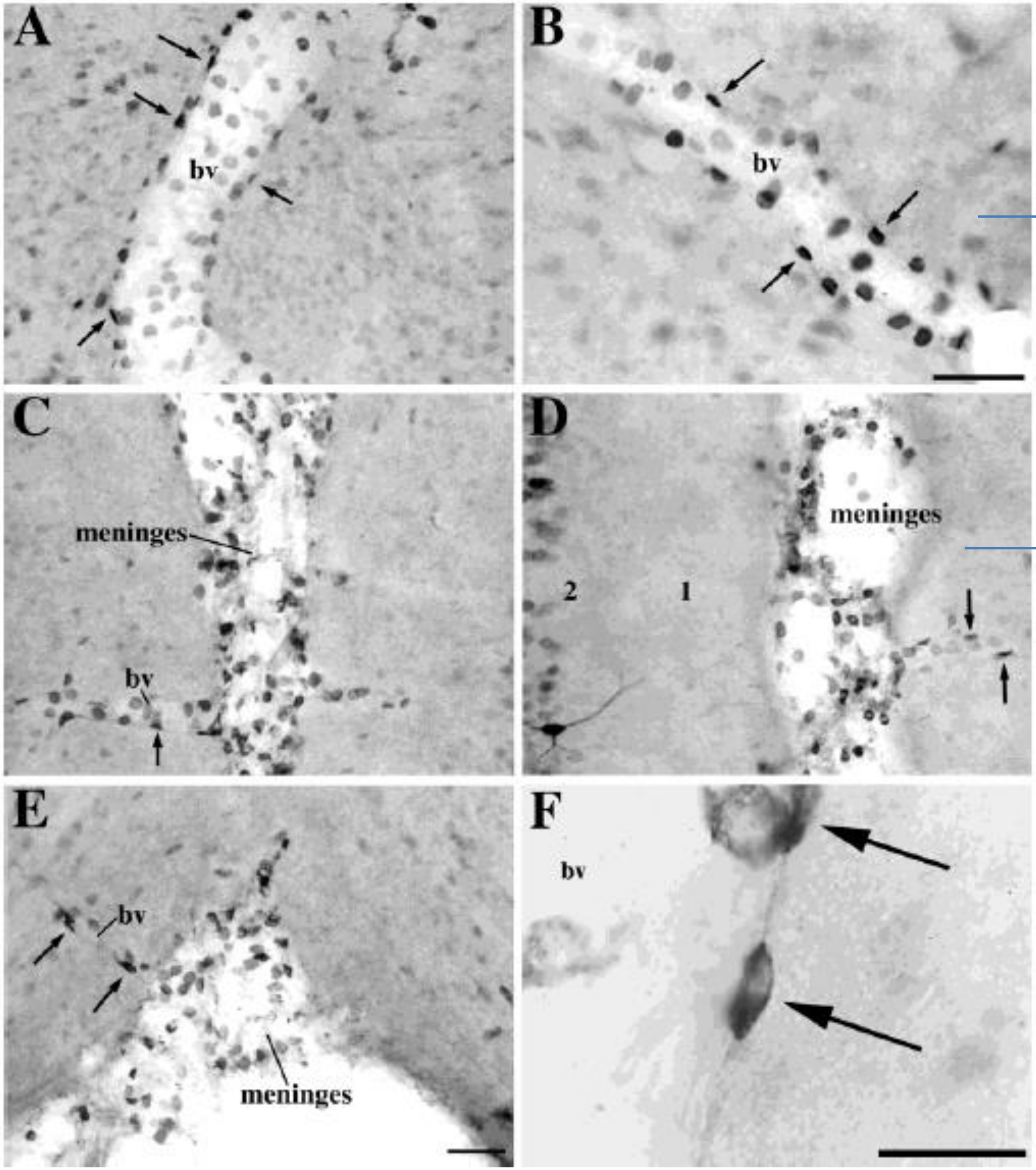
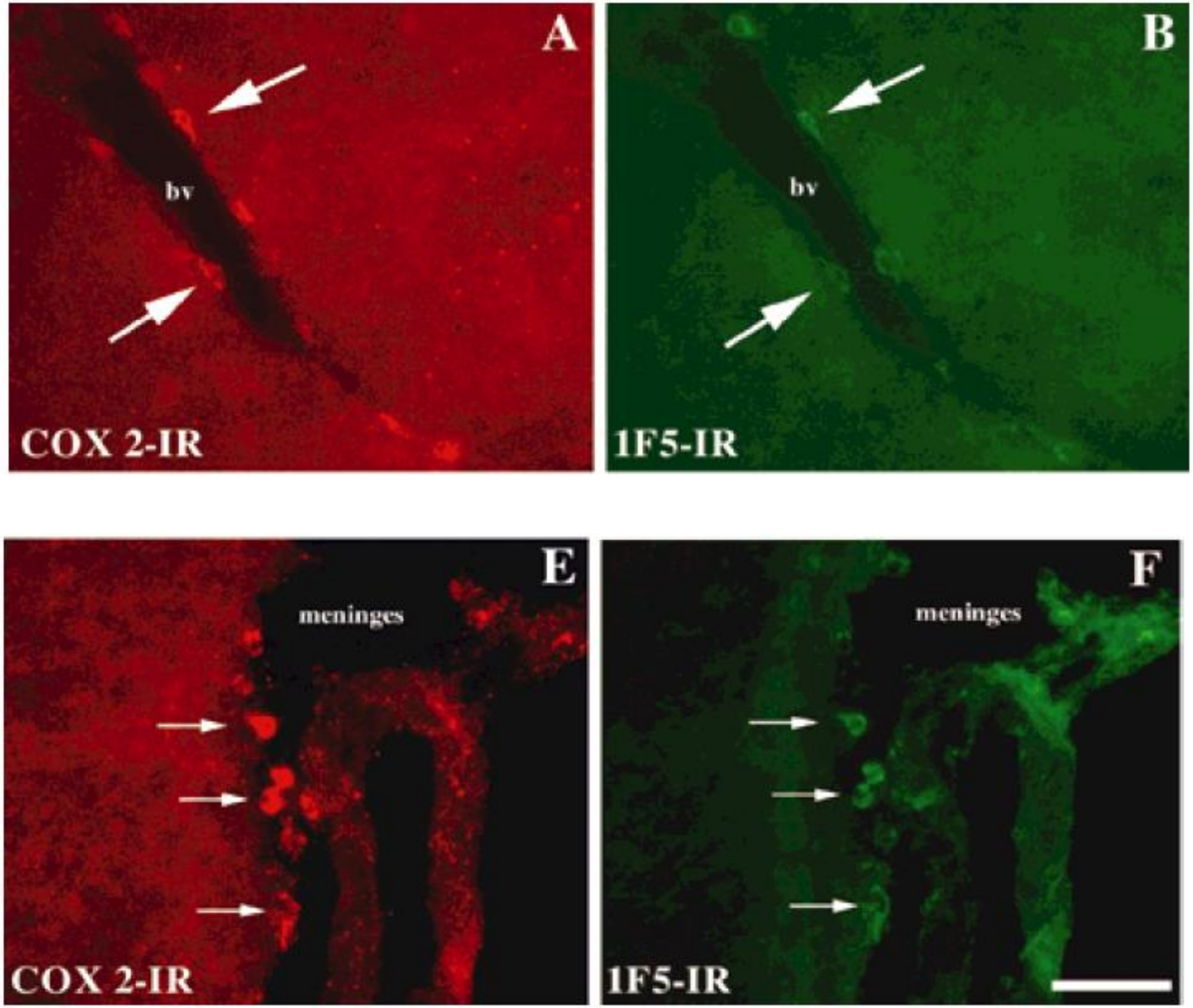
[3]Department of Pathology, Dartmouth Medical School, Lebanon, New Hampshire 03756
[4]Department of Biochemistry, Michigan State University, East Lansing, Michigan 48824

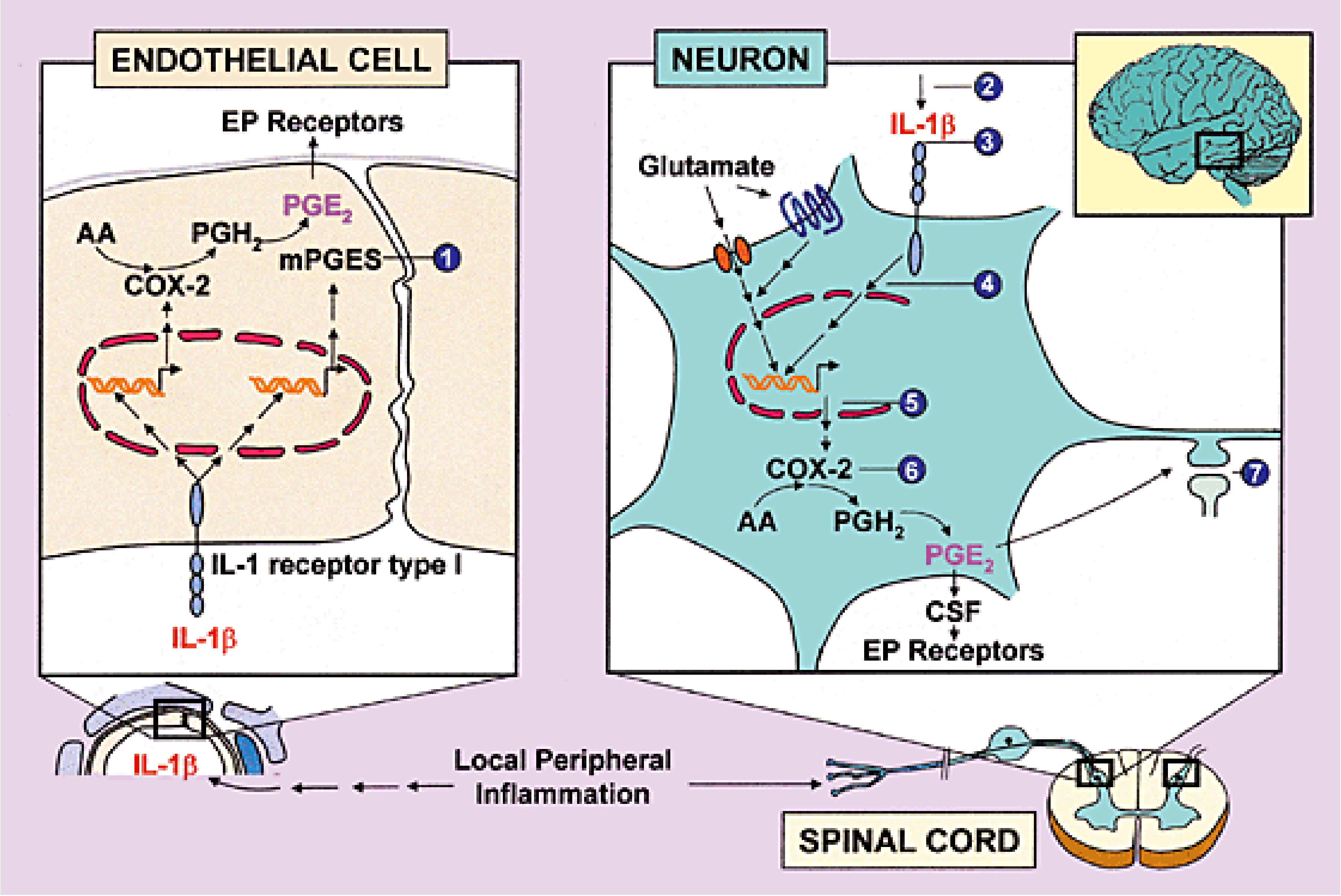

A
bv
B
bv
C
meninges
bv
D
meninges
2
1
E
bv
meninges
F
bv

NTS

córtex


A
bv
COX 2-IR
B
bv
1F5-IR
E
meninges
COX 2-IR
F
meninges
1F5-IR

Papel das PGE2 na neuroimunomodulação


ENDOTHELIAL CELL
EP Receptors
PGE$_2$
AA
PGH$_2$
mPGES
①
COX-2
IL-1 receptor type I
IL-1β
NEURON
②
IL-1β
③
Glutamate
④
⑤
COX-2
⑥
AA
PGH$_2$
PGE$_2$
⑦
CSF
EP Receptors
IL-1β
Local Peripheral Inflammation
SPINAL CORD

European Journal of Neuroscience, Vol. 27, pp. 3132–3150, 2008 doi:10.1111/j.1460-9568.2008.06296.x

Dual modulation of synaptic transmission in the nucleus tractus solitarius by prostaglandin E2 synthesized downstream of IL-1β

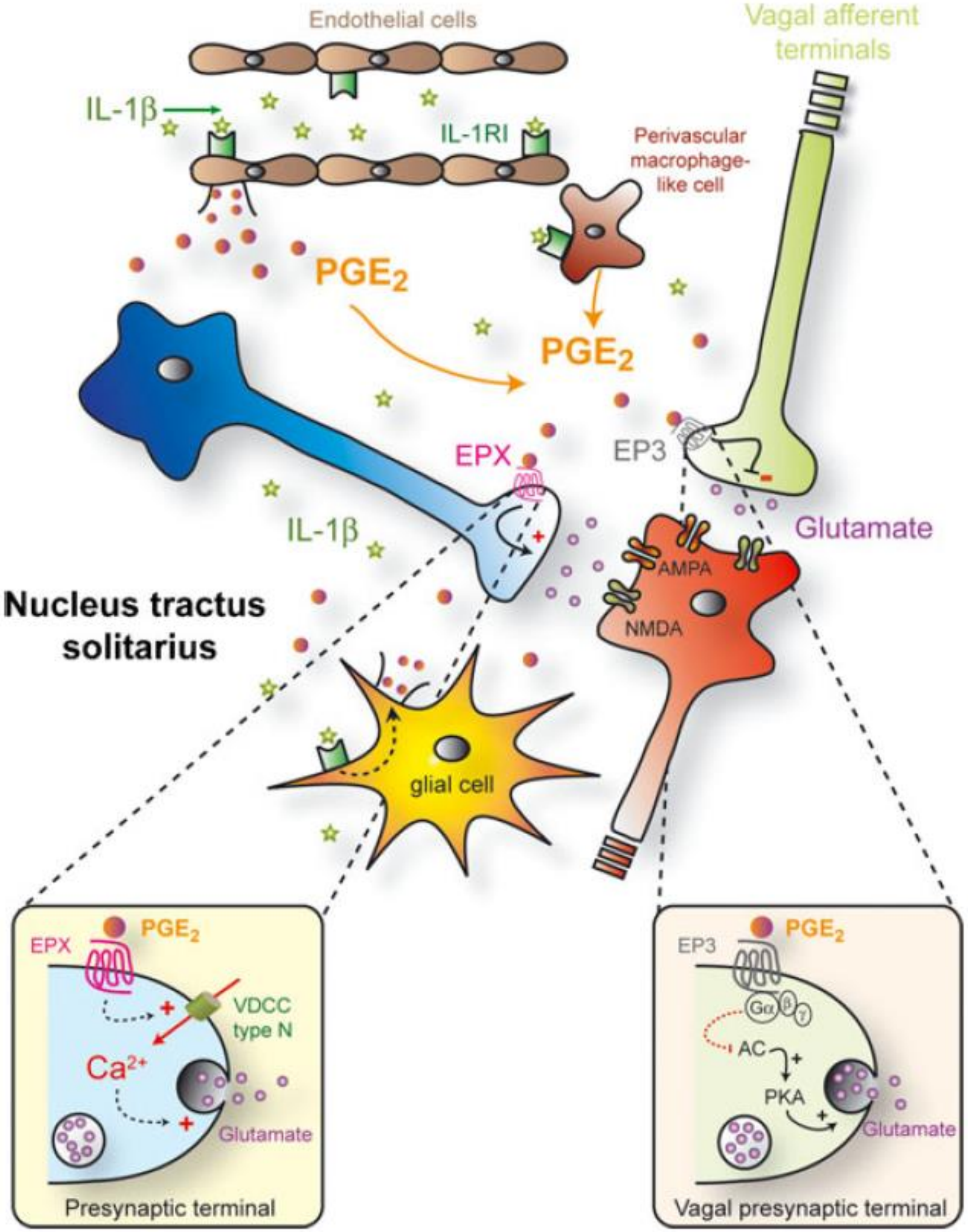
Vincent Marty, Mickaël El Hachmane and **Thierry Amédée**
Psychoneuroimmunology, Nutrition and Genetics (PsyNuGen), UMR 5226 CNRS-UB2/UMR 1286 INRA-UB2, Université Bordeaux 2, Institut François Magendie, 146 Rue Léo-Saignat, F-33077 Bordeaux, France

Keywords: brain stem slices, inflammation, nucleus tractus solitarius, PGE_2, synaptic transmission

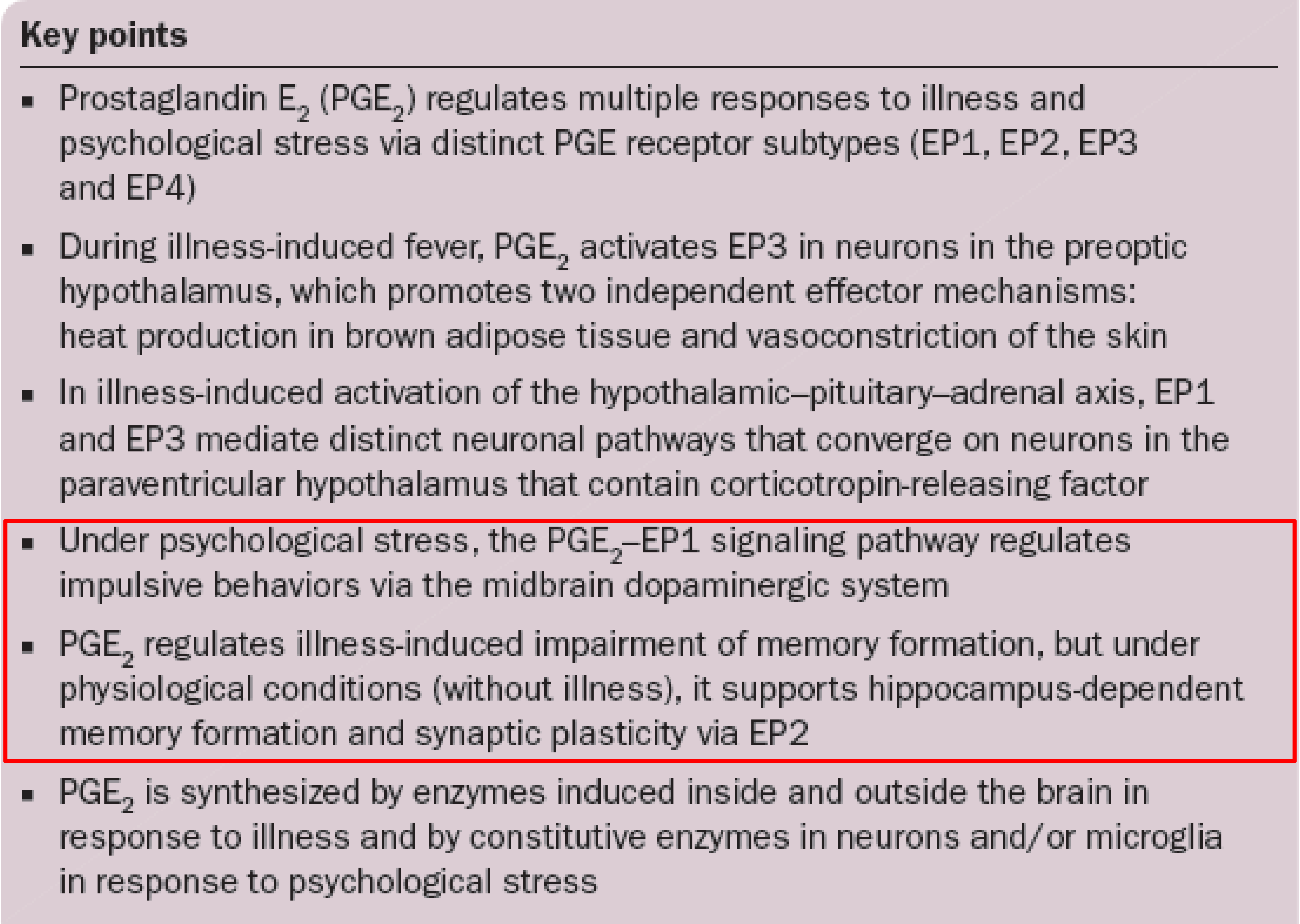
Abstract

The activation of the innate immune system induces the production of blood-borne proinflammatory cytokines like interleukin-1β (IL-1β), which in turn triggers brain-mediated adaptative responses referred to as sickness behaviour. These responses involve the modulation of neural networks in key regions of the brain. The nucleus tractus solitarius (NTS) of the brainstem is a key nucleus for immune-to-brain signalling. It is the main site of termination of vagal afferents and is adjacent to the area postrema, a circumventricular organ allowing blood-borne action of circulating IL-1β. Although it is well described that IL-1β activates cerebral endothelial and glial cells, it is still unknown if and how IL-1β or downstream-synthesized molecules impact NTS synaptic function. In this study we report that IL-1β did not modulate NTS synaptic transmission *per se*, whereas prostaglandin E_2 (PGE_2), which is produced downstream of IL-1β, produced opposite effects on spontaneous and evoked release. On the one hand, PGE_2 facilitated glutamatergic transmission between local NTS neurons by enhancing the frequency of spontaneous excitatory postsynaptic currents through a presynaptic receptor different from the classical EP1–4 subtypes. On the other hand, PGE_2 also depressed evoked excitatory input from vagal afferent terminals through presynaptic EP3 receptors coupled to G-proteins linked to adenylyl cyclase and protein kinase A activity. Our data show that IL-1β-induced PGE_2 can modulate evoked and spontaneous release in the NTS differentially through different mechanisms. These data unravel some molecular mechanisms by which innate immune stimuli could signal to, and be integrated within, the brainstem to produce central adaptative responses.

Papel das PGE2 na neuroimunomodulação


Endothelial cells
Vagal afferent terminals
IL-1β
IL-1RI
Perivascular macrophage-like cell
PGE_2
PGE_2
EPX
EP3
IL-1β
Glutamate
AMPA
NMDA
Nucleus tractus solitarius
glial cell
PGE_2
EPX
VDCC type N
Ca^{2+}
Glutamate
Presynaptic terminal
PGE_2
EP3
Gα β γ
AC
PKA
Glutamate
Vagal presynaptic terminal

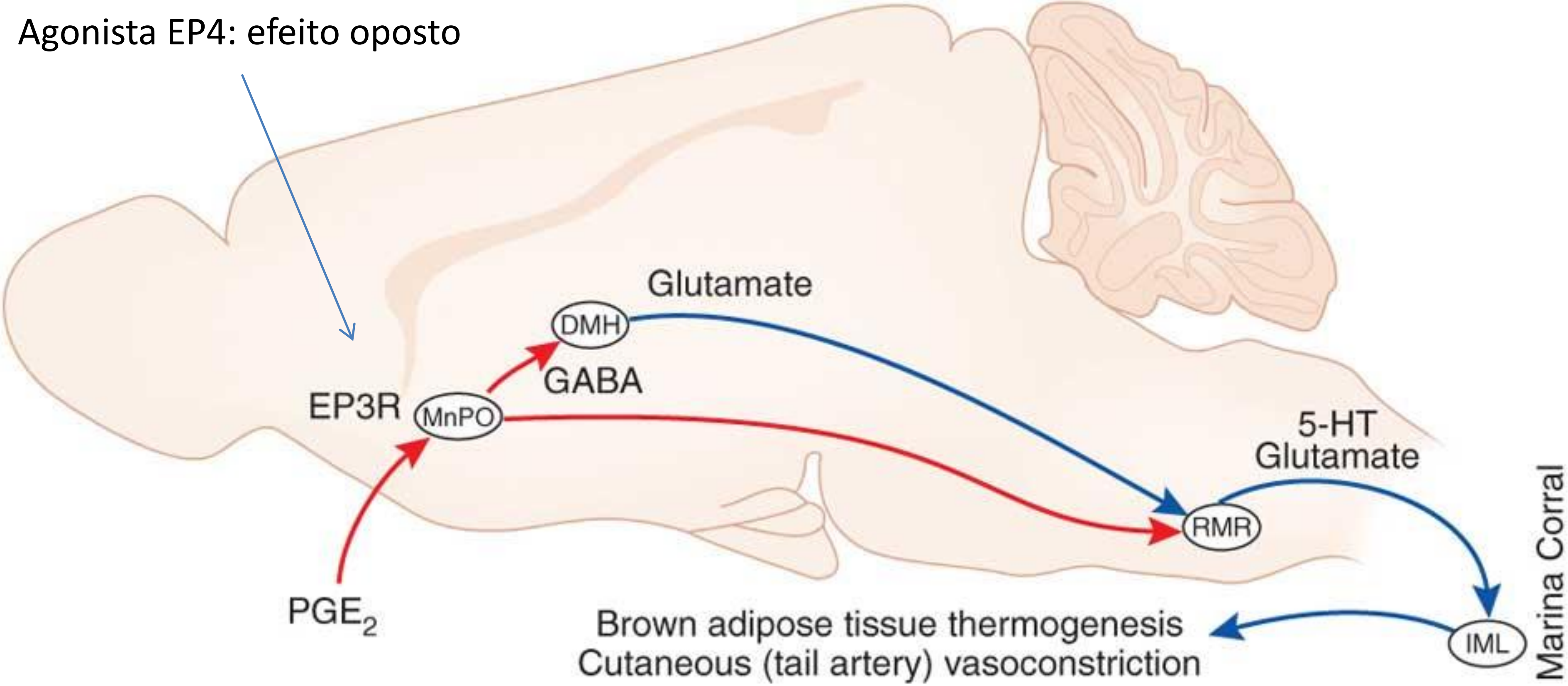
Papel das PGE2 na neuroimunomodulação



Key points

- Prostaglandin E_2 (PGE_2) regulates multiple responses to illness and psychological stress via distinct PGE receptor subtypes (EP1, EP2, EP3 and EP4)
- During illness-induced fever, PGE_2 activates EP3 in neurons in the preoptic hypothalamus, which promotes two independent effector mechanisms: heat production in brown adipose tissue and vasoconstriction of the skin
- In illness-induced activation of the hypothalamic–pituitary–adrenal axis, EP1 and EP3 mediate distinct neuronal pathways that converge on neurons in the paraventricular hypothalamus that contain corticotropin-releasing factor
- Under psychological stress, the PGE_2–EP1 signaling pathway regulates impulsive behaviors via the midbrain dopaminergic system
- PGE_2 regulates illness-induced impairment of memory formation, but under physiological conditions (without illness), it supports hippocampus-dependent memory formation and synaptic plasticity via EP2
- PGE_2 is synthesized by enzymes induced inside and outside the brain in response to illness and by constitutive enzymes in neurons and/or microglia in response to psychological stress

Papel das PGs- FEBRE


Agonista EP4: efeito oposto

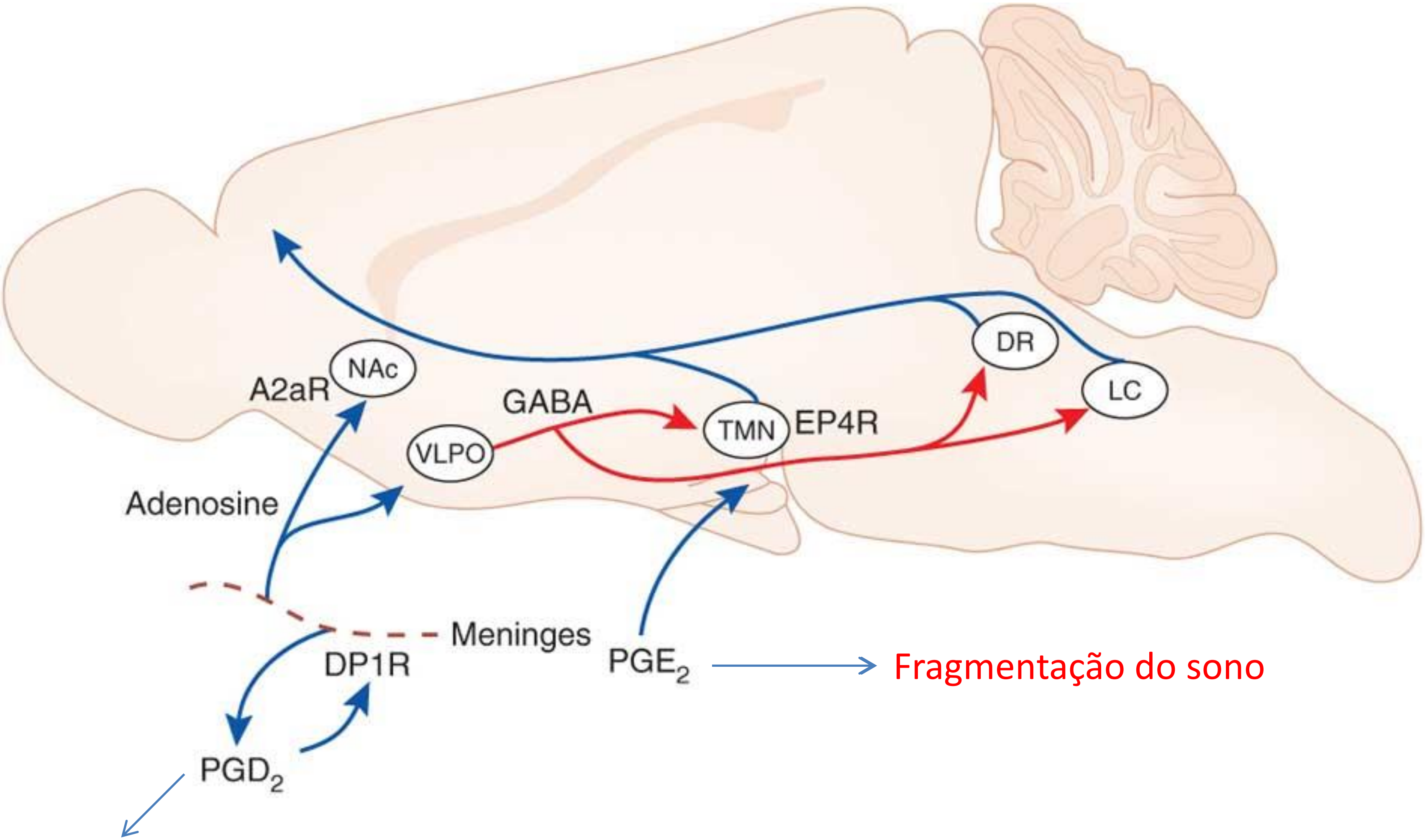
Glutamate
DMH
GABA
EP3R
MnPO
5-HT
Glutamate
RMR
PGE_2
Brown adipose tissue thermogenesis
Cutaneous (tail artery) vasoconstriction
IML
Marina Corral

PGE2 é produzida por células endoteliais e perivasculares ao longo de vênulas nas extremidades do cérebro, em especial, na área pré-optica do hipotálamo (controle da termogênesis).

MnPO: median preoptic nucleus
DMH: dorsomedial nucleus of the hypothalamus
RMR: rostral medullary raphe

Neural circuitry engaged by prostaglandins during the sickness Syndrome. Clifford B Saper, Andrej A Romanovsky & Thomas E Scammell Nature Neuroscience 15, 1088–1095 (2012).

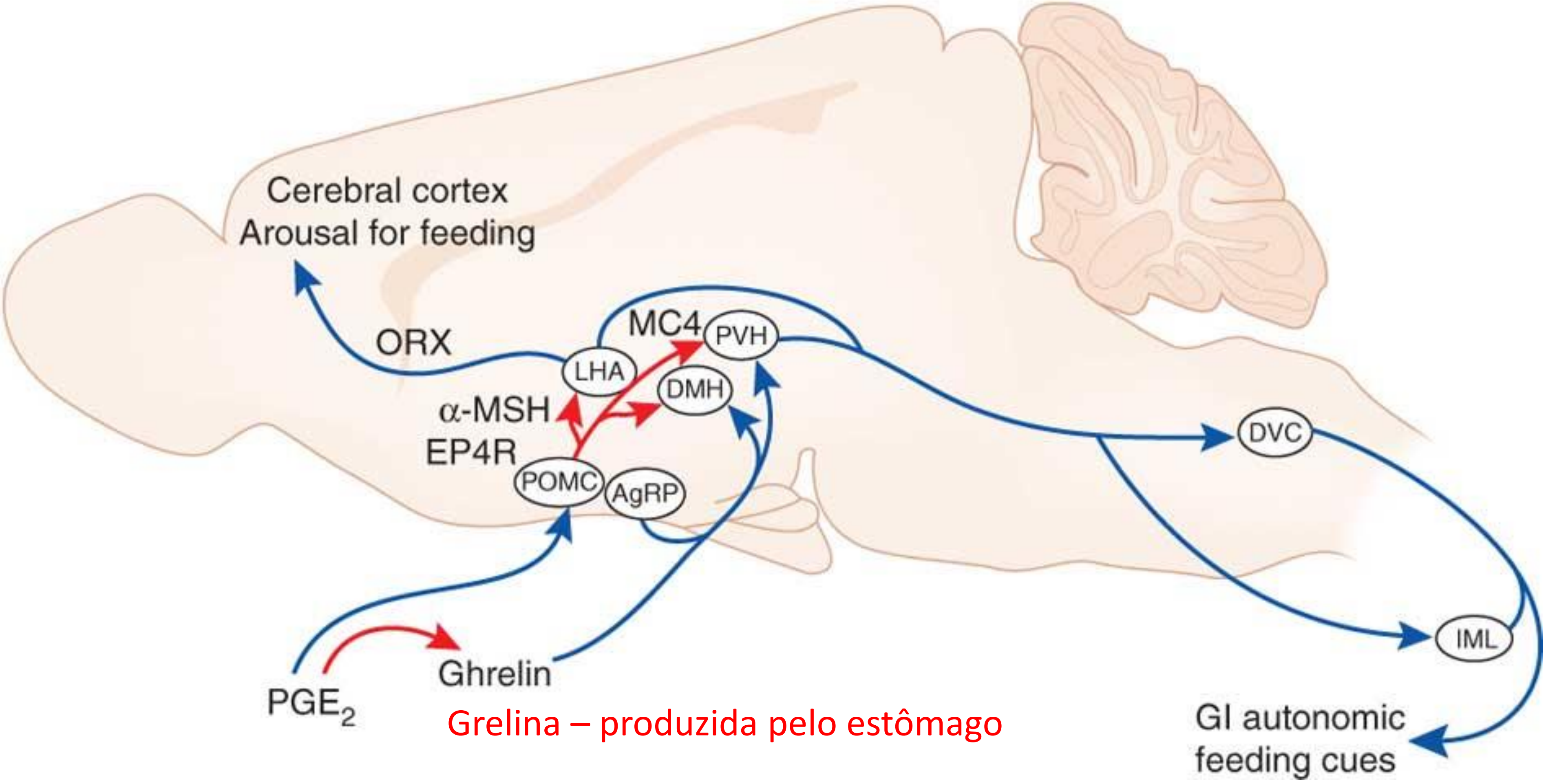
Papel das PGs- INDUÇÃO DO SONO


NAc
A2aR
GABA
VLPO
TMN
EP4R
DR
LC
Adenosine
Meninges
DP1R
PGE2
PGD2

Fragmentação do sono

NAc: núcleo accubens;
VLPO: ventrolateral preoptic nucleus: inibe sistema que controla o despertar (TMN: the histaminergic tuberomammillary nucleus, DR: dorsal raphe nucleus (DR), LC: noradrenergic locus coeruleus) induzindo o sono.

Papel das PGs- ANOREXIA



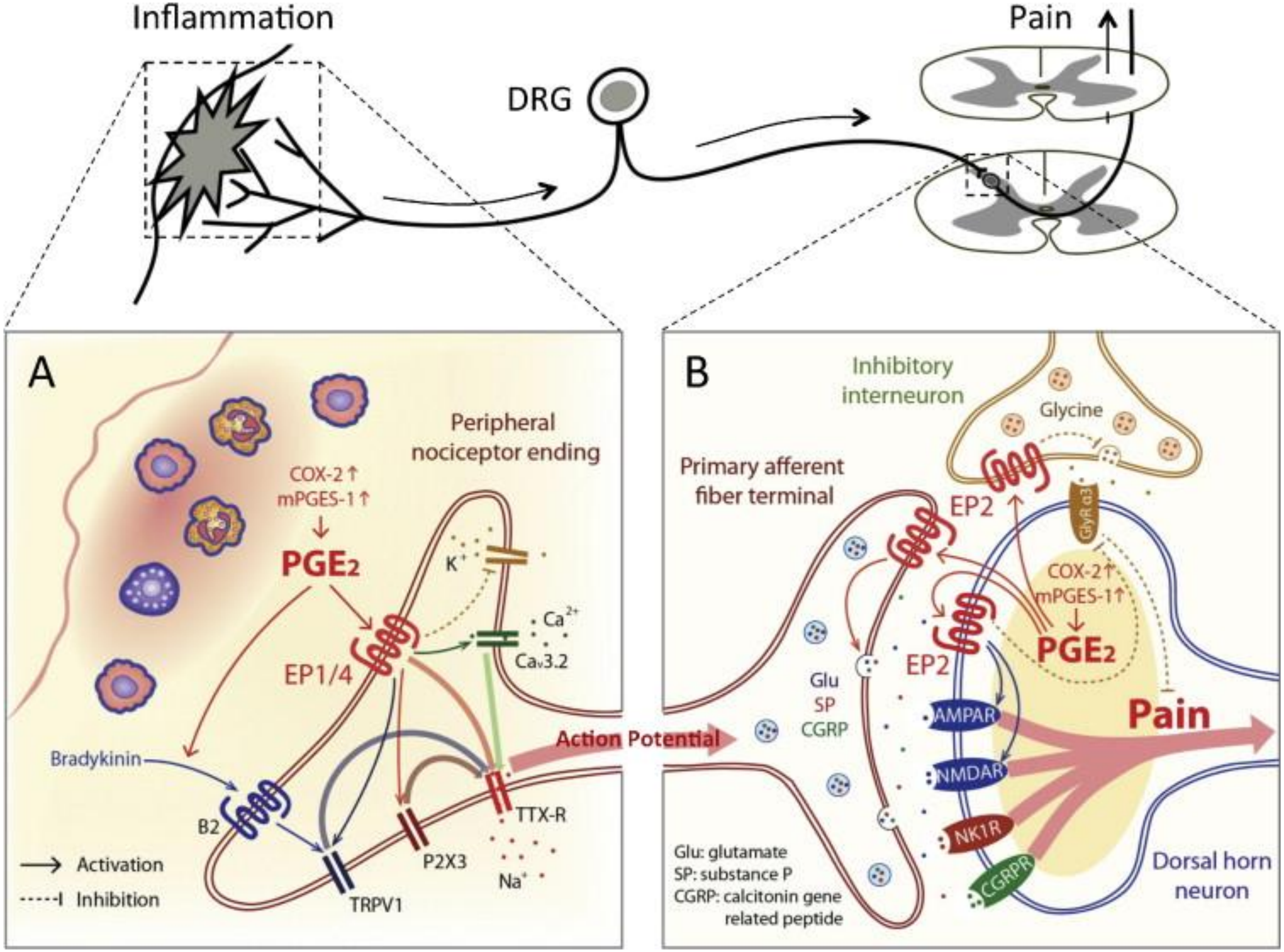
Cerebral cortex
Arousal for feeding
ORX
MC4
PVH
LHA
DMH
α-MSH
EP4R
POMC
AgRP
DVC
IML
PGE$_2$
Ghrelin
GI autonomic feeding cues

Grelina – produzida pelo estômago

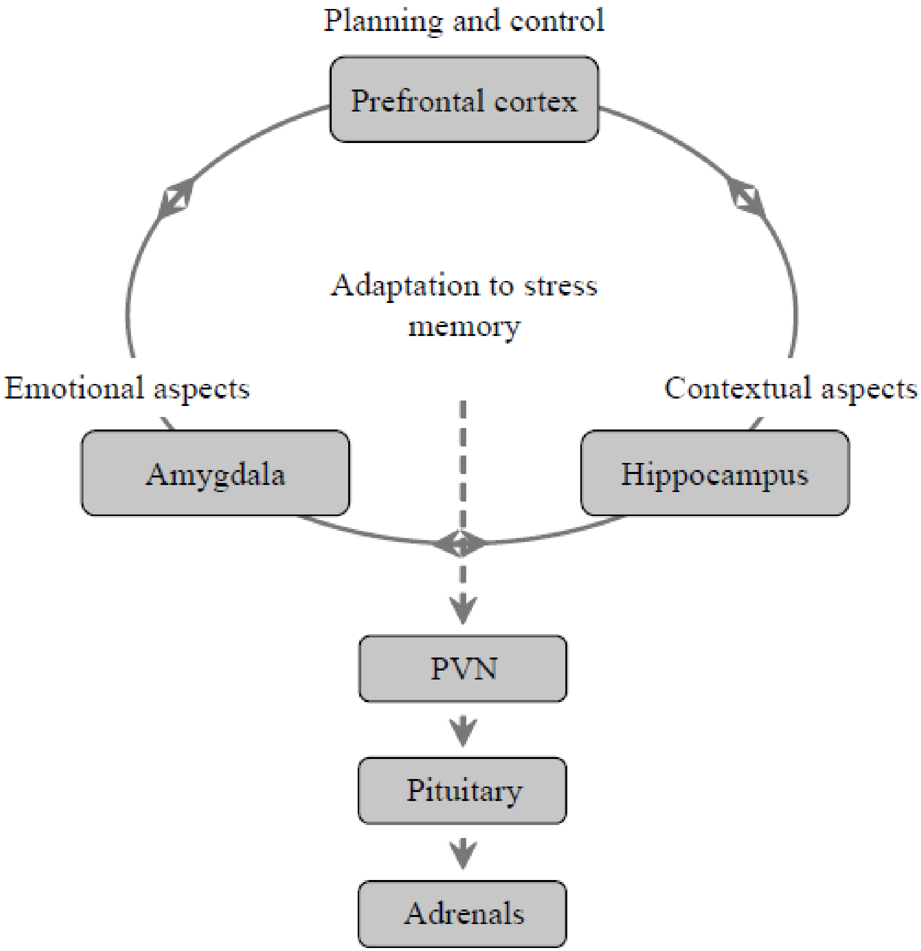
PGE2 produzida células vasculares e perivasculares da eminencia mediana ativa receptores EP4 em neurônios (proopiomelanocortin ,POMC) do núcleo arcuato.

Estas células produzem α-MSH (α-melanocyte stimulating hormone) que , atuando via recptores MC4 (melanocortin4) inibem neurônios do DMH, LHA (lateral hypothalamic area) e PVH (pareventricular nucleus) que promovem a alimentação.

Papel das PGs- DOR


Inflammation
DRG
Pain
A
Peripheral nociceptor ending
COX-2 ↑
mPGES-1 ↑
PGE₂
EP1/4
K⁺
Ca²⁺
Caᵥ3.2
Bradykinin
B2
TRPV1
P2X3
TTX-R
Na⁺
Action Potential
→ Activation
----I Inhibition
B
Inhibitory interneuron
Glycine
GlyR α3
Primary afferent fiber terminal
EP2
EP2
COX-2↑
mPGES-1↑
PGE₂
Glu
SP
CGRP
AMPAR
NMDAR
NK1R
CGRPR
Pain
Dorsal horn neuron
Glu: glutamate
SP: substance P
CGRP: calcitonin gene related peptide

Estresse



Planning and control

Prefrontal cortex

Adaptation to stress memory

Emotional aspects

Contextual aspects

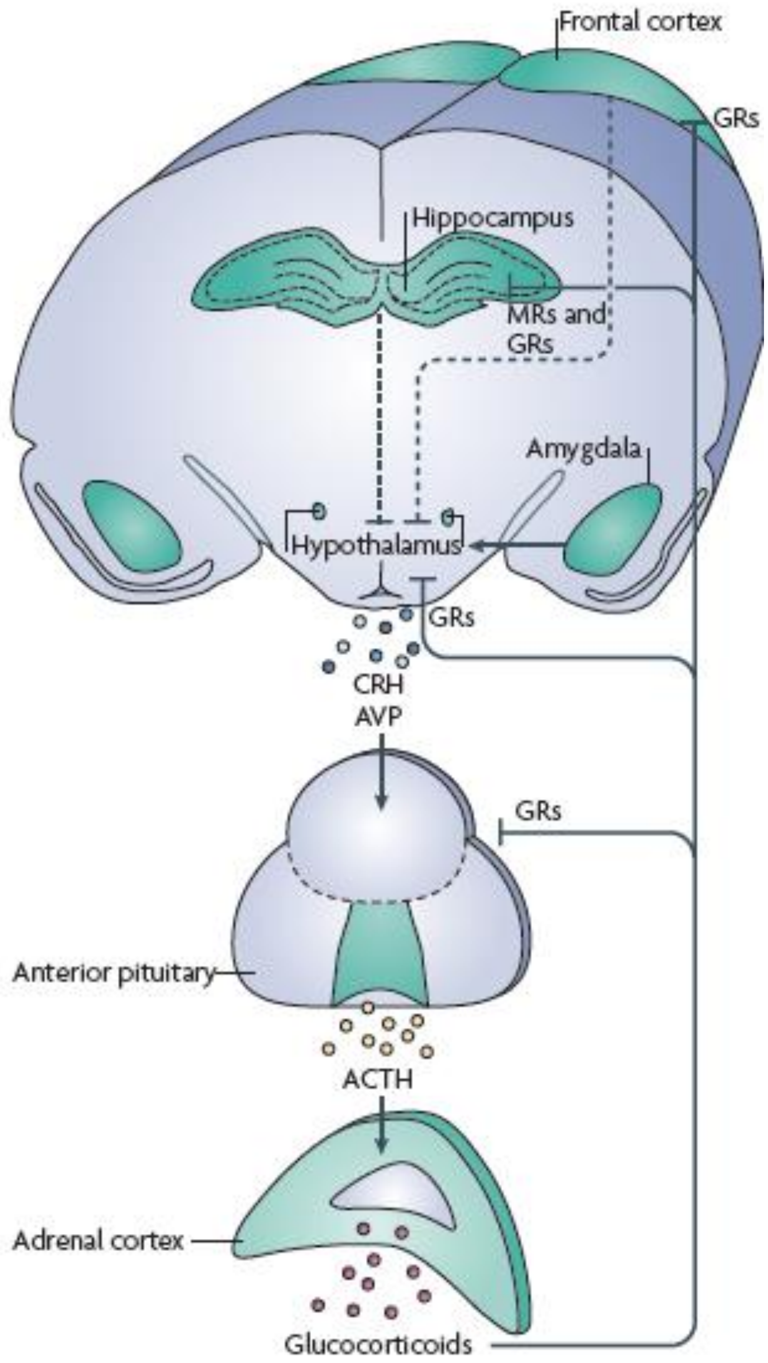
Amygdala

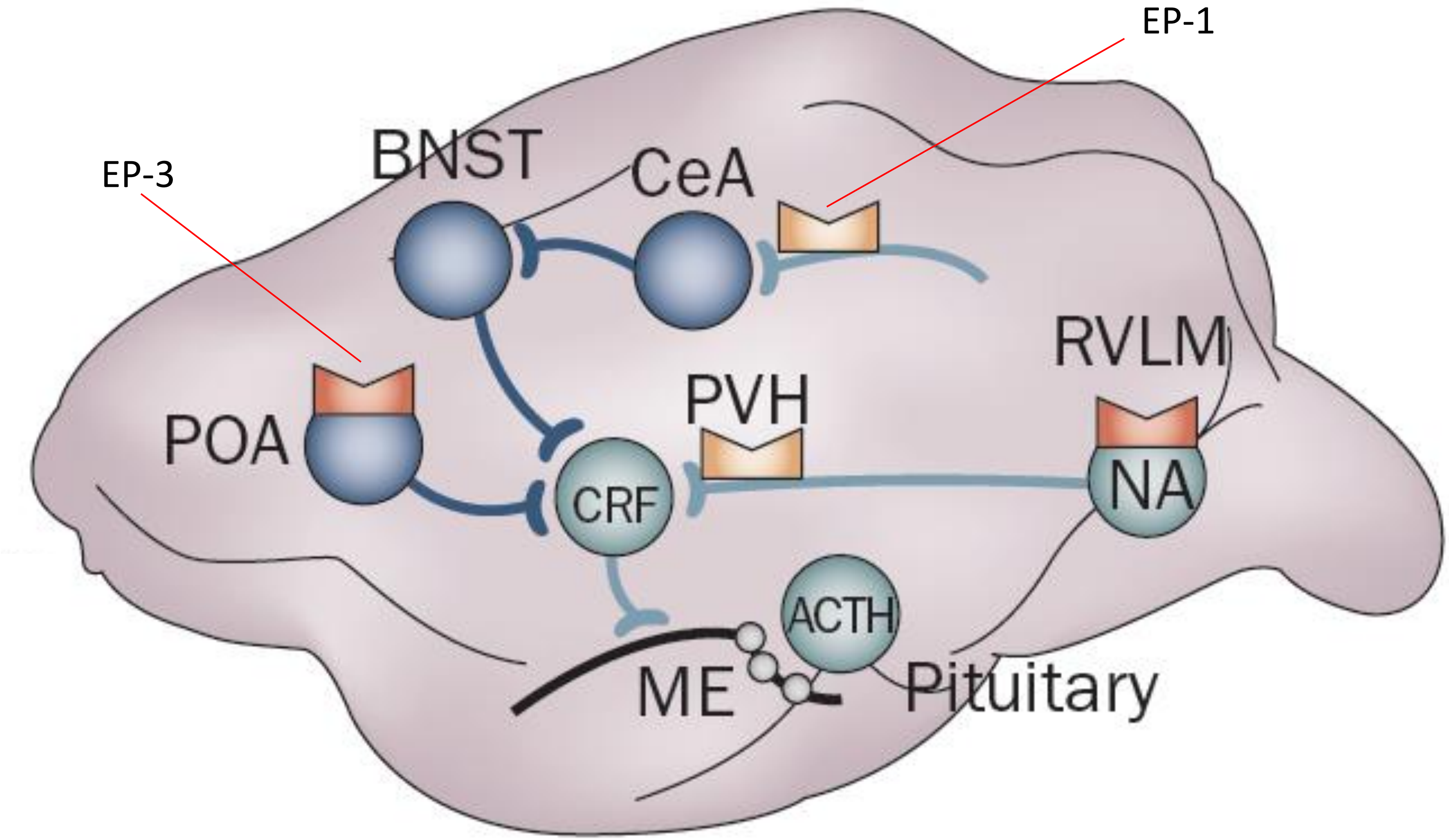
Hippocampus

PVN

Pituitary

Adrenals


Frontal cortex
GRs
Hippocampus
MRs and GRs
Amygdala
Hypothalamus
GRs
CRH
AVP
GRs
Anterior pituitary
ACTH
Adrenal cortex
Glucocorticoids


EP-1
EP-3
BNST
CeA
RVLM
PVH
POA
CRF
NA
ACTH
ME
Pituitary

RVLM, rostral ventrolateral medulla
POA, preoptic area
BNST, bed nucleus of the stria terminalis
CeA, central nucleus of the amygdala
PVH, paraventricular

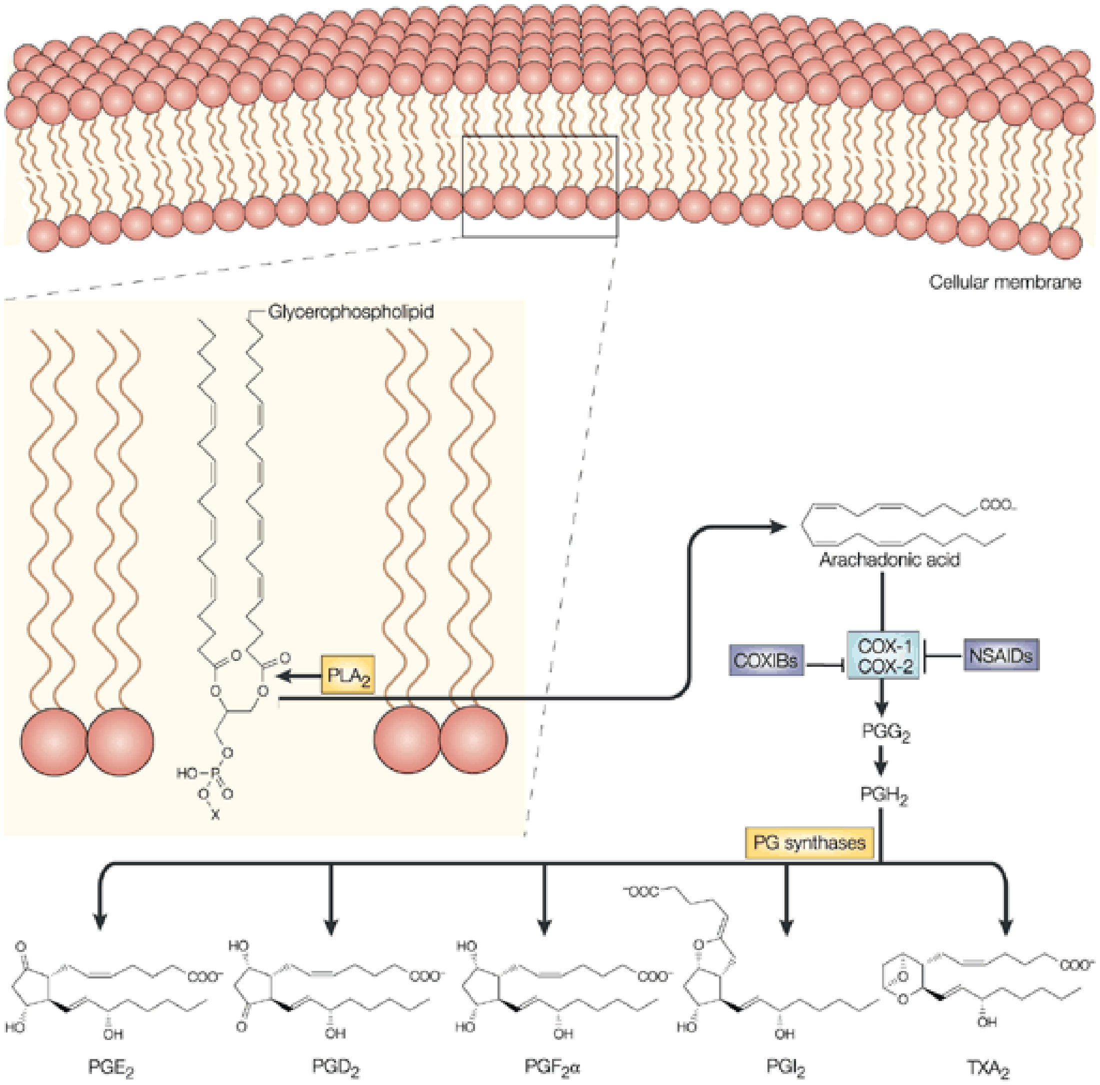
NSAIDs: Bloqueiam a ativação do eixo HPA

Efeitos dos glicocorticóides - Sistema Nervoso

IL-1β induz produção de prostanglandinas no sistema nervosos central

(reflexo imunológico)

PGE2 induz a febre e alterações comportamentais ativando o núcleo preóptico medial


Cellular membrane
Glycerophospholipid
HO–P
O
X
PLA$_2$
COO$^-$
Arachadonic acid
COXIBs
COX-1
COX-2
NSAIDs
PGG$_2$
PGH$_2$
PG synthases
PGE$_2$
PGD$_2$
PGF$_{2\alpha}$
PGI$_2$
TXA$_2$
HO
OH

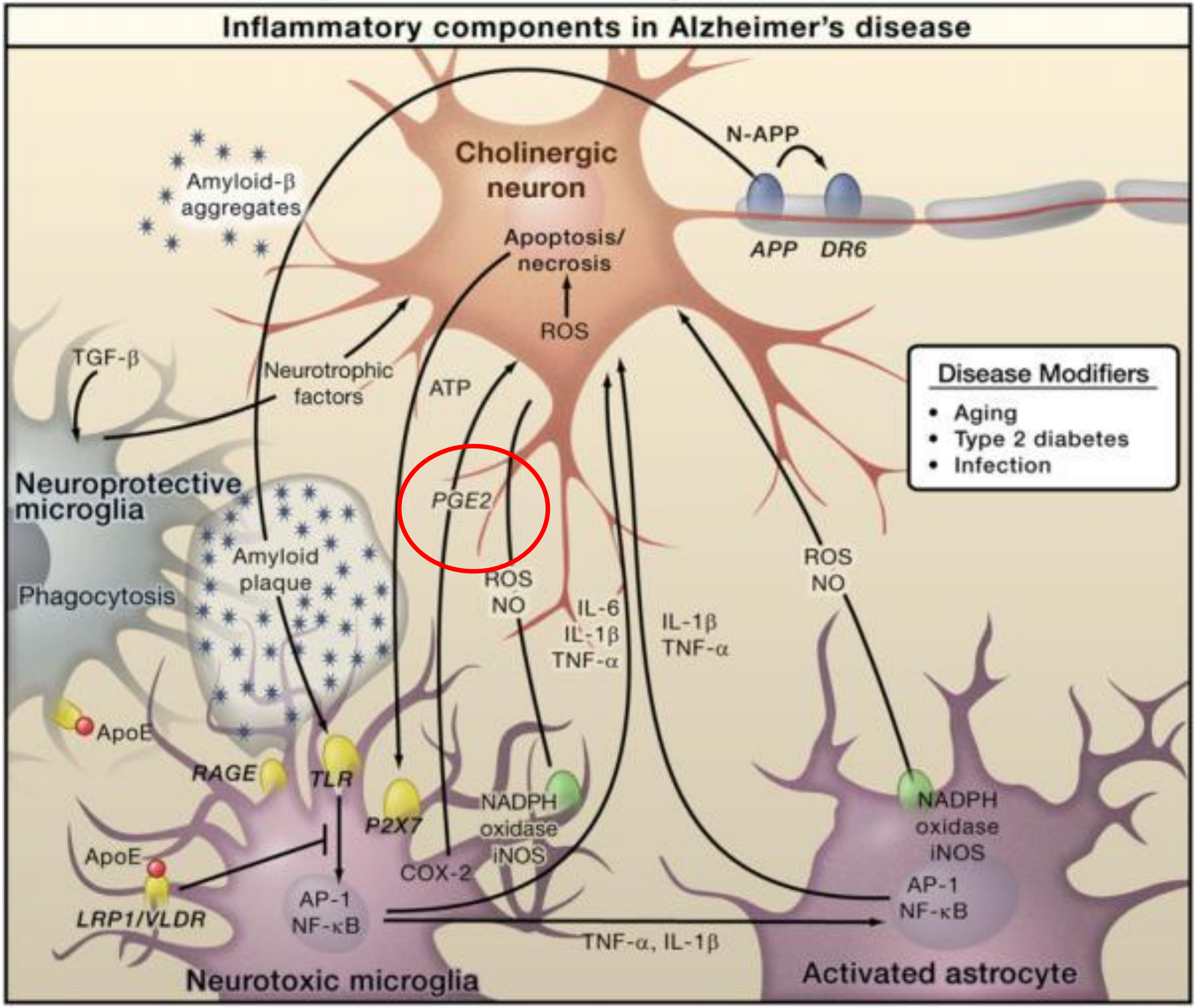
Nature Reviews | Cancer

Glicocorticóides inibem PLA2 e COX

Table 1. Reported changes of COX-1 and COX-2 in neurodegenerative diseases

Disorder	COX-1	COX-2
AD	Small trial with indomethacin (preferential COX-1 inhibitor) beneficial in protecting from cognitive decline. Use of aspirin (preferential COX-1 inhibitor) associated with reduced risk of AD. Increased COX-1-expressing microglia surrounding amyloid plaques.	Upregulation of COX-2 in early AD, and downregulation in advanced AD stages. Randomized trials with COX-2-selective inhibitors not effective.
PD	COX-1 expression unchanged by MPTP, but >65% of ventral midbrain PGE$_2$ originated from COX-1. Aspirin (preferential COX-1 inhibitor) and mixed COX inhibitors neuroprotective in parkinsonian models.	COX-2 expressed within dopaminergic neurons of substantia nigra in the PD postmortem brain. COX-2 induced in the MPTP model of PD during destruction of nigrostriatal pathway. COX-2-selective inhibitors neuroprotective in parkinsonian models.
TBI	Accumulation of COX-1 expressing microglia at peri-lesional areas and in the developing core in patients with TBI.	Conflicting reports on COX-2-selective inhibitors in experimental TBI: nimesulide reversed motor and cognitive abnormalities; celecoxib worsened motor but not cognitive performance; and rofecoxib did not limit neuronal cell death. No difference in lesion volume 3 weeks after TBI and no changes in Morris water maze performance in *COX-2*-null versus wild-type mice.
Prion diseases	Accumulation of COX-1-expressing microglia in areas of severe tissue damage and around vacuoles in CJD patients.	Not determined.
HIV dementia	Twofold increase in *COX-1* mRNA expression in the demented versus non-demented patients.	*COX-2* mRNA expression is unchanged.
Stroke	*COX-1* deletion increases vulnerability to focal cerebral ischemia. COX-1 inhibition reduced neuronal injury and oxidative stress in hippocampus during transient global ischemia.	COX-2 expression upregulated in neurons in early ischemia. COX-2 inhibition or genetic deletion reduces infarct volume and neurological deficits.
ALS	COX-1, and not COX-2, is the primary source of PGE$_2$ in spinal cords of SOD1^{G93A} mice. However, deletion of *COX-1* does not improve preservation of motor neurons and survival of transgenic mutant mice.	Levels of *COX-2* mRNA and PGE$_2$ increased in mutant SOD1 mice. Selective COX-2 inhibitors (celecoxib and rofecoxib) improve motor performance, extend survival and reduce CSF levels of PGE$_2$. COX-2 expression increased in motor neurons, interneurons and glial cells in seven human sporadic ALS patients. Double-blinded, placebo-controlled clinical trial with celecoxib (800 mg/day) administered for 12 months in ALS subjects did not show any beneficial effect.
MS	Not determined.	No correlation between PGE$_2$ and clinical scores of MS severity or biomarkers of axonal or astroglial injury.

Inflamação e Doença de Alzheimer


Inflammatory components in Alzheimer's disease
Cholinergic neuron
Apoptosis/ necrosis
ROS
N-APP
APP
DR6
Amyloid-β aggregates
TGF-β
Neurotrophic factors
ATP
PGE2
Neuroprotective microglia
Phagocytosis
Amyloid plaque
ROS NO
IL-6 IL-1β TNF-α
IL-1β TNF-α
ROS NO
Disease Modifiers
• Aging
• Type 2 diabetes
• Infection
ApoE
RAGE
TLR
P2X7
NADPH oxidase iNOS
COX-2
ApoE
LRP1/VLDR
AP-1 NF-κB
TNF-α, IL-1β
NADPH oxidase iNOS
AP-1 NF-κB
Neurotoxic microglia
Activated astrocyte

Fonte: Glass et al., Cell. 2010 Mar 19;140(6):918-34.