HOSPITAL MOINHOS DE VENTO
INSTITUTO DE EDUCAÇÃO E PESQUISA
CURSO INTERDISCIPLINAR DE DOR E CUIDADOS PALIATIVOS

ANATOMIA E FISIOLOGIA DA DOR (FISIOPATOLOGIA DA DOR)

André P. Schmidt, MD, PhD, TSA/SBA
Co-responsável pelo CET do Serviço de Anestesia e Medicina Perioperatória do Hospital de Clínicas de Porto Alegre.
Serviço de Transplante Hepático do HCPA e da Santa Casa de Porto Alegre.
Membro da Equipe SAGIN de Anestesiologia.
Clínica de Dor do Hospital Moinhos de Vento.
SOS Dor - Centro Clínico do Hospital Mãe de Deus.
Pesquisador Orientador - Departamento de Bioquímica da UFRGS e Disciplina de Anestesiologia da FMUSP.

Estrutura da Disciplina

Conteúdo programático:

1. Embriologia da dor
2. Neuroanatomia das vias dolorosas
3. Fisiopatologia da dor
4. Mecanismos neuroquímicos da transmissão dolorosa
5. Pesquisa básica em fisiopatologia da dor

Estrutura da Disciplina

- Objetivos gerais
- Importância do tema
- Conceituação geral
- Epidemiologia básica
- Introdução geral
- Neuroanatomia da dor:
  - Desenvolvimento anatômico do sistema nociceptivo
  - Embriologia da Dor
  - Anatomia das unidades nociceptivas
  - Anatomia das unidades supressoras da dor
- Neurofisiologia da dor:
  - Desenvolvimento neuroquímico da dor
  - Mecanismos neuroquímicos da transmissão dolorosa
- Discussão

OBJETIVOS GERAIS

OBJETIVOS GERAIS

- Parte 1 – Conceitos gerais sobre a fisiopatologia da dor
- Parte 2 – Desenvolvimento das vias dolorosas
- Parte 3 – Neuroanatomia das vias nociceptivas ascendentes e descendentes
- Parte 4 – Mecanismos neuroquímicos da dor
- Parte 5 – Neuromodulação da dor
- Parte 6 – Fisiopatologia da dor – Pesquisa básica
- Parte 7 – Fontes bibliográficas em Dor

CONCEITOS GERAIS

Transmissão Dolorosa

- Definição: “Dor é uma experiência sensorial e emocional desagradável associada a dano tecidual real ou potencial, ou descrita em termos de tais danos”
- Dor: Resposta variável, individual, sem fundamental relação com estímulo nocivo – Componente Genético
  - Mecanismos que modulam a dor (analgesia)
  - Plasticidade neuronal

Belknap et al., Life Sciences 1995; 57 :117-124

Hain et al., J Pharmacol Exp Ther 1999; 291: 444-449

EPIDEMIOLOGIA BÁSICA E IMPORTÂNCIA DA DOR

Estudo da dor

- Dor crônica – até 46,5 % da população
- Custos altos (U$100 bilhões)
- Dores refratárias a tratamentos convencionais

  Fibromialgia

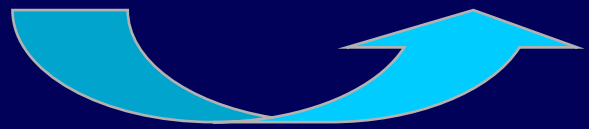
  SDRC

  Neuralgia pós-herpética

  Dor lombar

  Dor facial

  Cefaléia



Novas Alternativas Terapêuticas

Edwards RR, Neurology 2005; 65:437-442.

Importância da Pesquisa e Estudos em Dor

"Dos pacientes internados, com ou sem cirurgia, 87% tem algum tipo de dor, e 33% tem dor a maior parte do tempo"

Bruster S. BMJ 1994; 309:1542-46.

Seguimento de pacientes pós-toracotomia

Incidência de dor persistente

80% em 3 meses

75% em 6 meses

61% em 12 meses

Até 30% dos pacientes submetidos a herniorrafia relatam dor persistente por 3 meses

Perttunen et al. *Acta Anaesthesiol Scand.* 1999;43:563-567

Poobalan et al. *Br J Surg.* 2001;88:1122-1126.

Pesquisa em Dor

ÚLTIMOS 5 ANOS

– Grande Produção Científica

> 50 mil trabalhos

(Ensaios clínicos e Metanálises)

↓ investimento em Pesquisas

INTRODUÇÃO GERAL

Histórico da pesquisa em Dor

- Descoberta do nociceptor
  - Sherrington, C. S. *The Integrative Action of the Nervous System* (Scribner, New York, 1906).
- Publicação da Teoria de Melzack e Wall (1965)
  - Interesse dos Pesquisadores de área básica
- Aumento dos Programas de Tratamento da Dor
- Fundação da IASP e criação do periódico Pain

Histórico da pesquisa em Dor

MELZACK R, STOTLER WA, LIVINGSTON WK.

Effects of discrete brainstem lesions in cats on perception of noxious stimulation.

J Neurophysiol 1958 Jul;21(4):353-67.

MELZACK R, WALL PD.

On the nature of cutaneous sensory mechanisms.

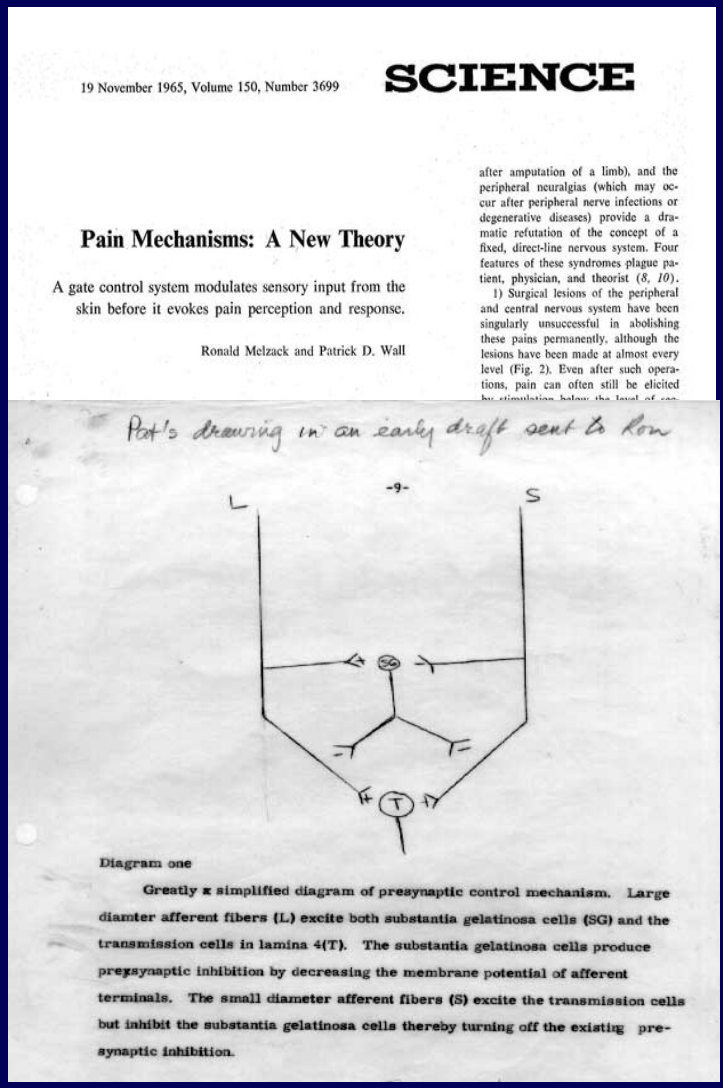
Brain 1962 Jun;85:331-56

WALL PD.

Presynaptic control of impulses at the first central synapse in the cutaneous pathway.

Prog Brain Res 1964;12:92-118.

Teoria de Melzack e Wall



19 November 1965, Volume 150, Number 3699 **SCIENCE**

Pain Mechanisms: A New Theory

A gate control system modulates sensory input from the skin before it evokes pain perception and response.

Ronald Melzack and Patrick D. Wall

after amputation of a limb), and the peripheral neuralgias (which may occur after peripheral nerve infections or degenerative diseases) provide a dramatic refutation of the concept of a fixed, direct-line nervous system. Four features of these syndromes plague patient, physician, and theorist (*8, 10*).

1) Surgical lesions of the peripheral and central nervous system have been singularly unsuccessful in abolishing these pains permanently, although the lesions have been made at almost every level (Fig. 2). Even after such operations, pain can often still be elicited

Pat's drawing in an early draft sent to Ron

-9-

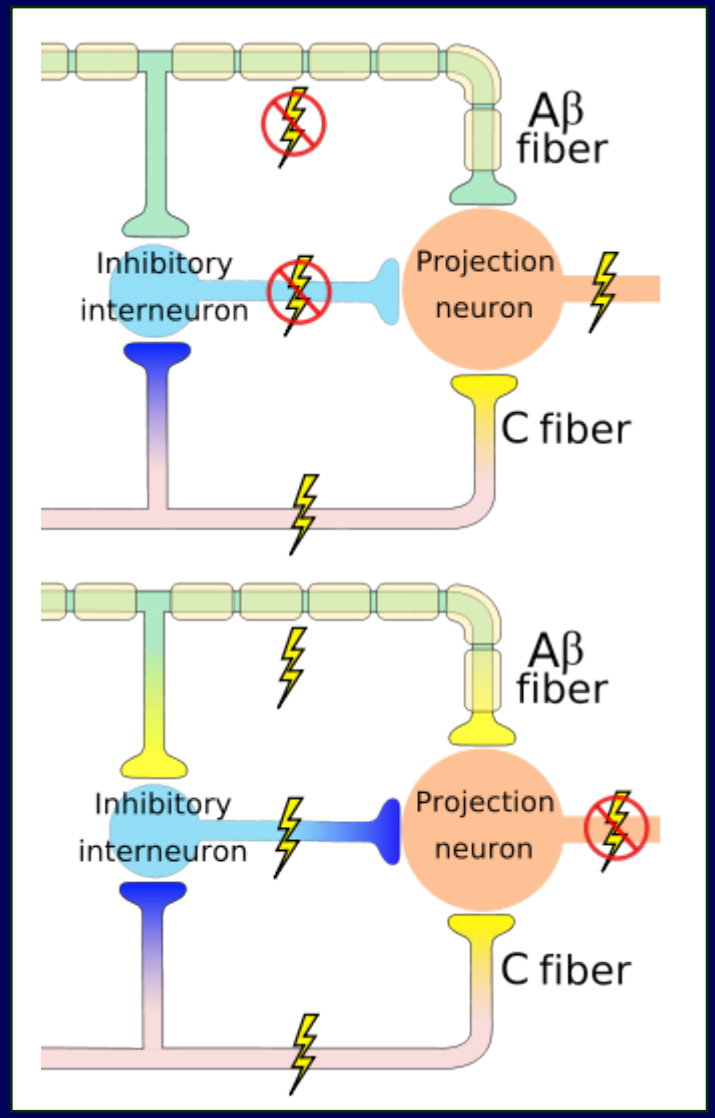
L S SG T

Diagram one

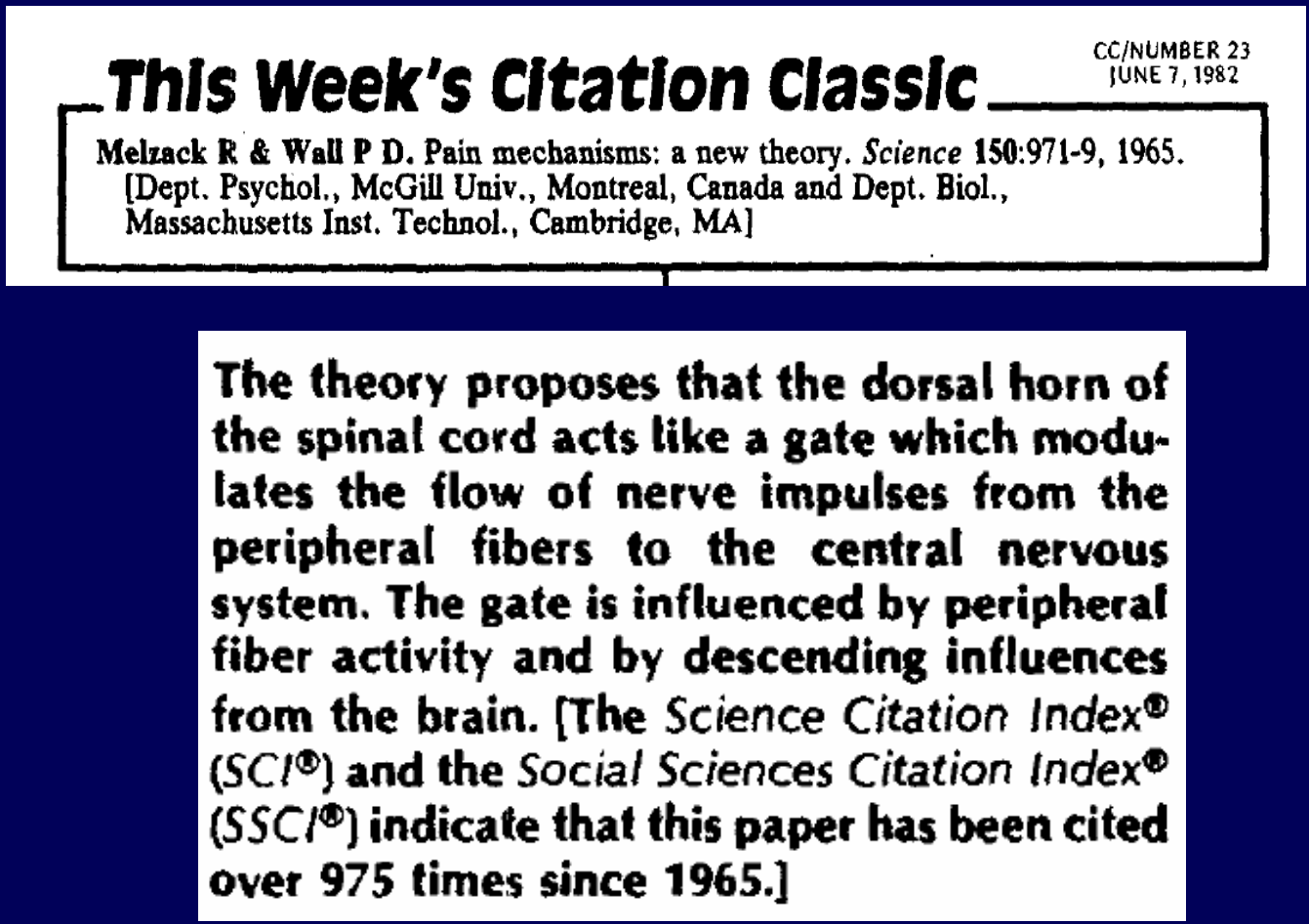
Greatly x simplified diagram of presynaptic control mechanism. Large diamter afferent fibers (L) excite both substantia gelatinosa cells (SG) and the transmission cells in lamina 4(T). The substantia gelatinosa cells produce presynaptic inhibition by decreasing the membrane potential of afferent terminals. The small diameter afferent fibers (S) excite the transmission cells but inhibit the substantia gelatinosa cells thereby turning off the existing presynaptic inhibition.

Ronald Melzack

Patrick D. Wall



Histórico da pesquisa em Dor



This Week's Citation Classic

CC/NUMBER 23
JUNE 7, 1982

Melzack R & Wall P D. Pain mechanisms: a new theory. *Science* 150:971-9, 1965.
[Dept. Psychol., McGill Univ., Montreal, Canada and Dept. Biol., Massachusetts Inst. Technol., Cambridge, MA]

The theory proposes that the dorsal horn of the spinal cord acts like a gate which modulates the flow of nerve impulses from the peripheral fibers to the central nervous system. The gate is influenced by peripheral fiber activity and by descending influences from the brain. [The *Science Citation Index*® (*SCI*®) and the *Social Sciences Citation Index*® (*SSCI*®) indicate that this paper has been cited over 975 times since 1965.]

COMPONENTES DA DOR

Nocicepção

Percepção da dor

Sofrimento

Comportamento de dor

TIPOS DE DOR

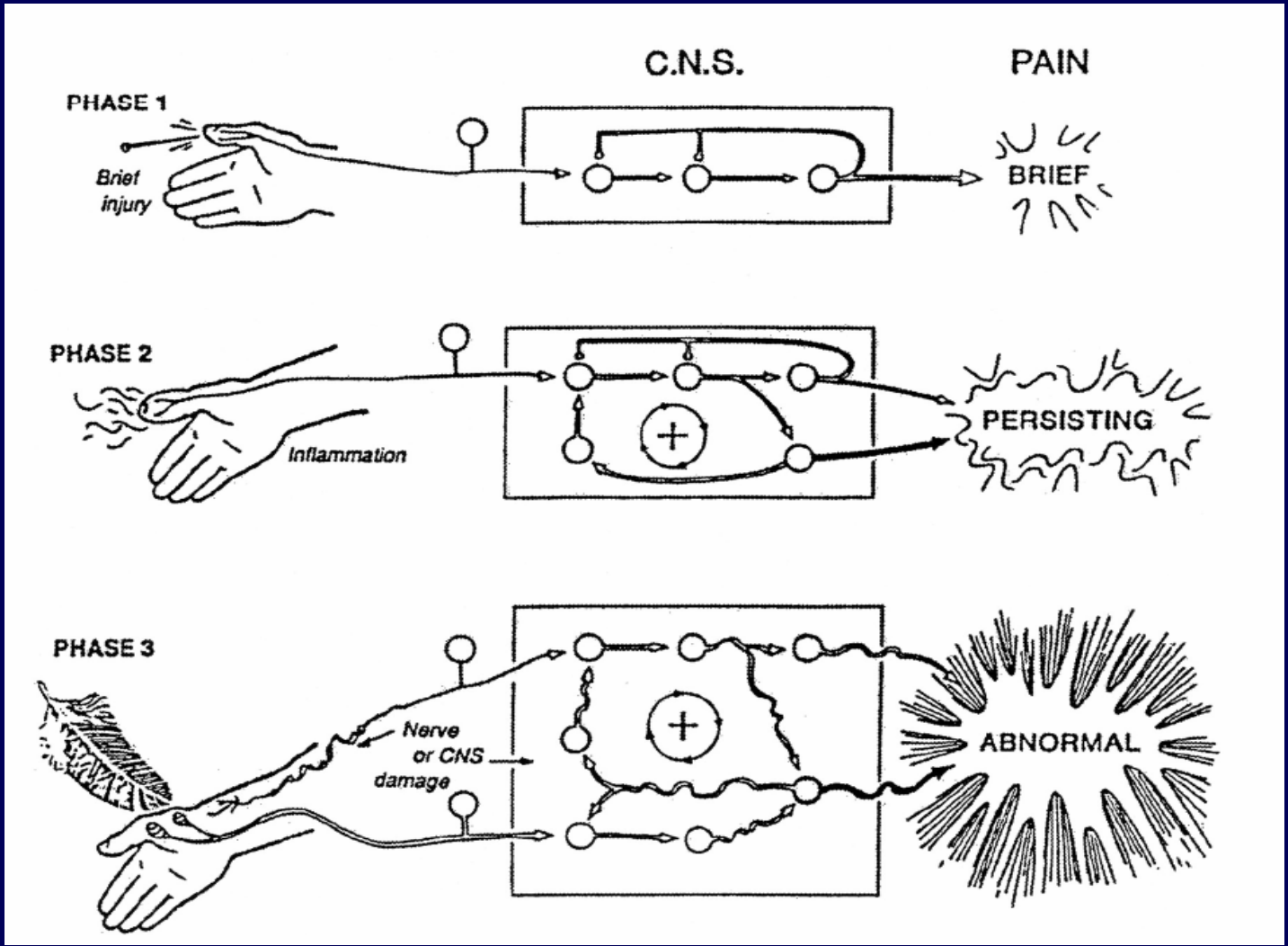
Dor eventual

Dor aguda

Dor crônica

Loeser and Melzack, Lancet 1999; 353:1607-9

TIPOS DE DOR



Hill RG, The Neuroscientist 2001; 7:282-92.

TERMOS TÉCNICOS EM DOR

Dor nociceptiva

Dor neurogênica

Dor neuropática

Dor psicogênica

Antinocicepção = analgesia

Hiperalgesia primária vs. secundária

Alodinia

Parestesia - Disestesia

Millan MJ, Prog Neurobiol 1999; 57:1-164.

DISCUSSÃO DE ARTIGO

Pain

Pain: an overview

John D Loeser, Ronald Melzack

Lancet 1999; **353:** 1607–09

Until the 1960s, pain was considered an inevitable sensory response to tissue damage. There was little room for the affective dimension of this ubiquitous experience, and none whatsoever for the effects of genetic differences, past experience, anxiety, or expectation. In recent years, great advances have been made in our understanding of the mechanisms that underlie pain and in the treatment of people who complain of pain. The roles of factors outside the patient's body have also been clarified. Pain is probably the most common symptomatic reason to seek medical consultation. All of us have headaches, burns, cuts, and other pains at some time during childhood and adult life. Individuals who undergo surgery are almost certain to have postoperative pain. Ageing is also associated with an increased likelihood of chronic pain. Health-care expenditures for chronic pain are enormous, rivalled only by the costs of wage replacement and welfare programmes for those who do not work because of pain. Despite improved knowledge of underlying mechanisms and better treatments, many people who have chronic pain receive inadequate care.

DESENVOLVIMENTO DO SISTEMA NOCICEPTIVO

- *Surgimento dos nociceptores (IG = 7 sem)*

- *Distribuição completa dos nociceptores e formação completa dos neurônios (IG = 20 sem)*

- *Imaturidade – fibras pouco mielinizadas*

- *Papel do tronco encefálico (IG = 24 sem)*

- *Desenvolvimento corno dorsal (IG = 6 sem início e IG = 30 sem término)*

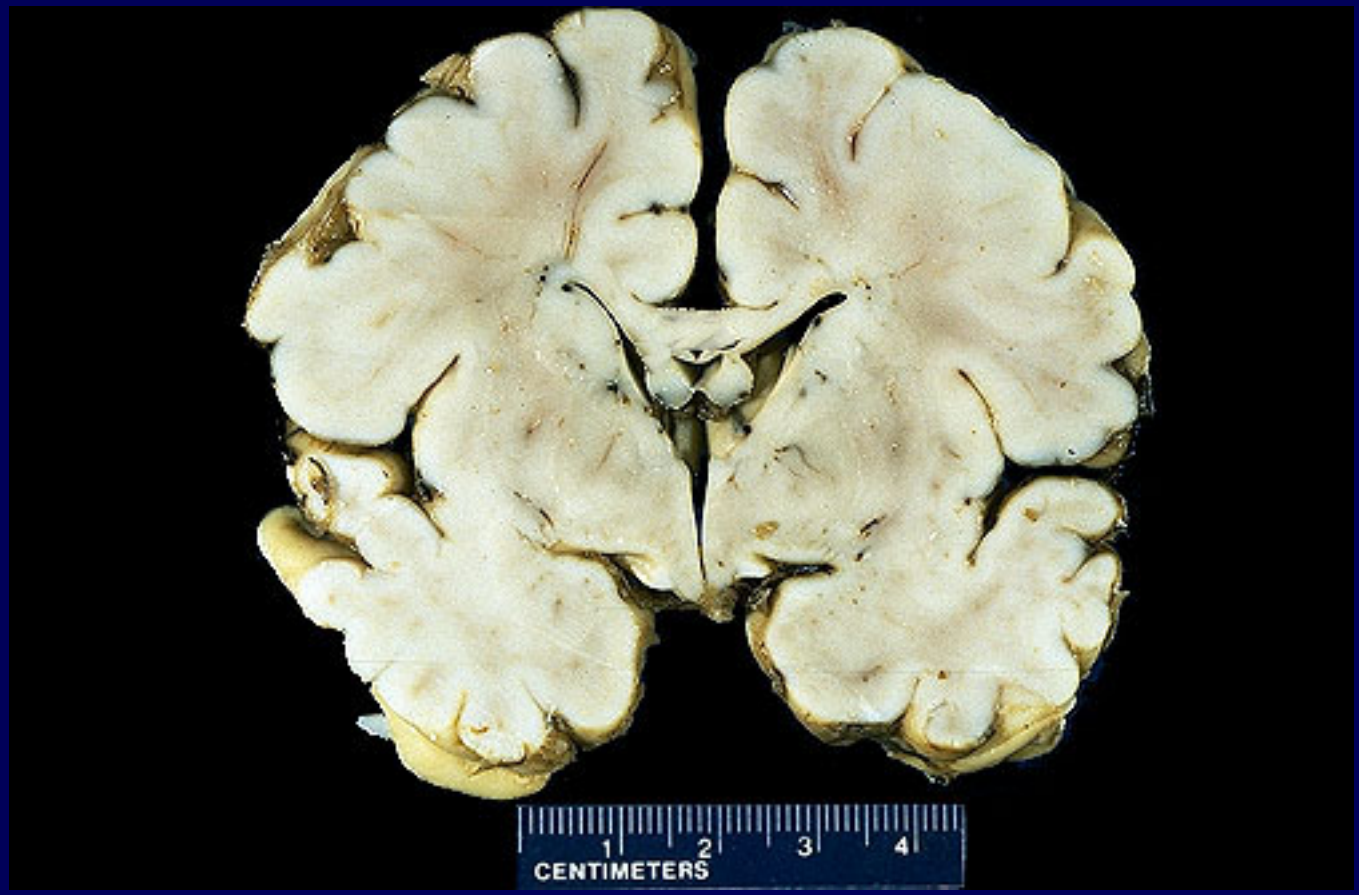
- *Desenvolvento do neocórtex (IG = 8 sem início e IG = 20 sem término)*

- *Estabelecimento de conexões tálamo-corticais (IG = 22-26 sem)*

- *Maturação completa das vias dolorosas – primeira infância*

Anand and Hickley. N Engl J Med 1987; 317:1321-1329.

Neuroanatomia da dor



DESENVOLVIMENTO COMPORTAMENTAL DA DOR

- *Inclinação tátil da cabeça após estímulo perioral (IG = 7 sem)*
- *Mãos sensíveis ao toque (IG = 10 sem)*
- *Movimentos organizados (IG = 14-24 sem)*
- *Ciclo sono-vigília (IG = 24-28 sem)*
- *Resposta a estímulos acústicos (IG = 25 sem)*
- *Resposta à luz e expressão facial específica à dor (IG = 26 sem)*

Craig et al. Pain 1993; 52:287-99.

DESENVOLVIMENTO NEUROQUÍMICO DA DOR

- *Indução precoce de apoptose após redução da atividade neuronal*
- *Substância P, glutamato e PDGC*
- *Papel das neurotrofinas*
    - *Fator de Crescimento Neural (NGF) - TrkA*
    - *BDNF*
    - *GDNF*
    - *NT-3*
- *Vulnerabilidade das vias nociceptivas no período neonatal*

Mattheson et al. J Neurobiol 1997; 32:22-32.

DESENVOLVIMENTO NEUROQUÍMICO DA DOR

- *Receptores Opióides – Início e distribuição dinâmica*
- *Receptores Glutamatérgicos*
- *Receptores para Neurocininas – Substância P*
- *Receptores Serotoninérgicos*
- *Receptores Purinérgicos*
- *Receptores GABAérgicos*

Peptídeos em formação (IG 8 – 14 sem)

Sistemas de estresse (SNA) – (IG 10 sem)

Anand and Hickley. N Engl J Med 1987; 317:1321-1329.

DESENVOLVIMENTO NEUROQUÍMICO DA DOR

- *Neurotransmissores:*

  - *Medula espinhal (IG = 8 – 16 sem) – SP, PDGC, glutamato, neurocinina-A, neuropeptídeos*

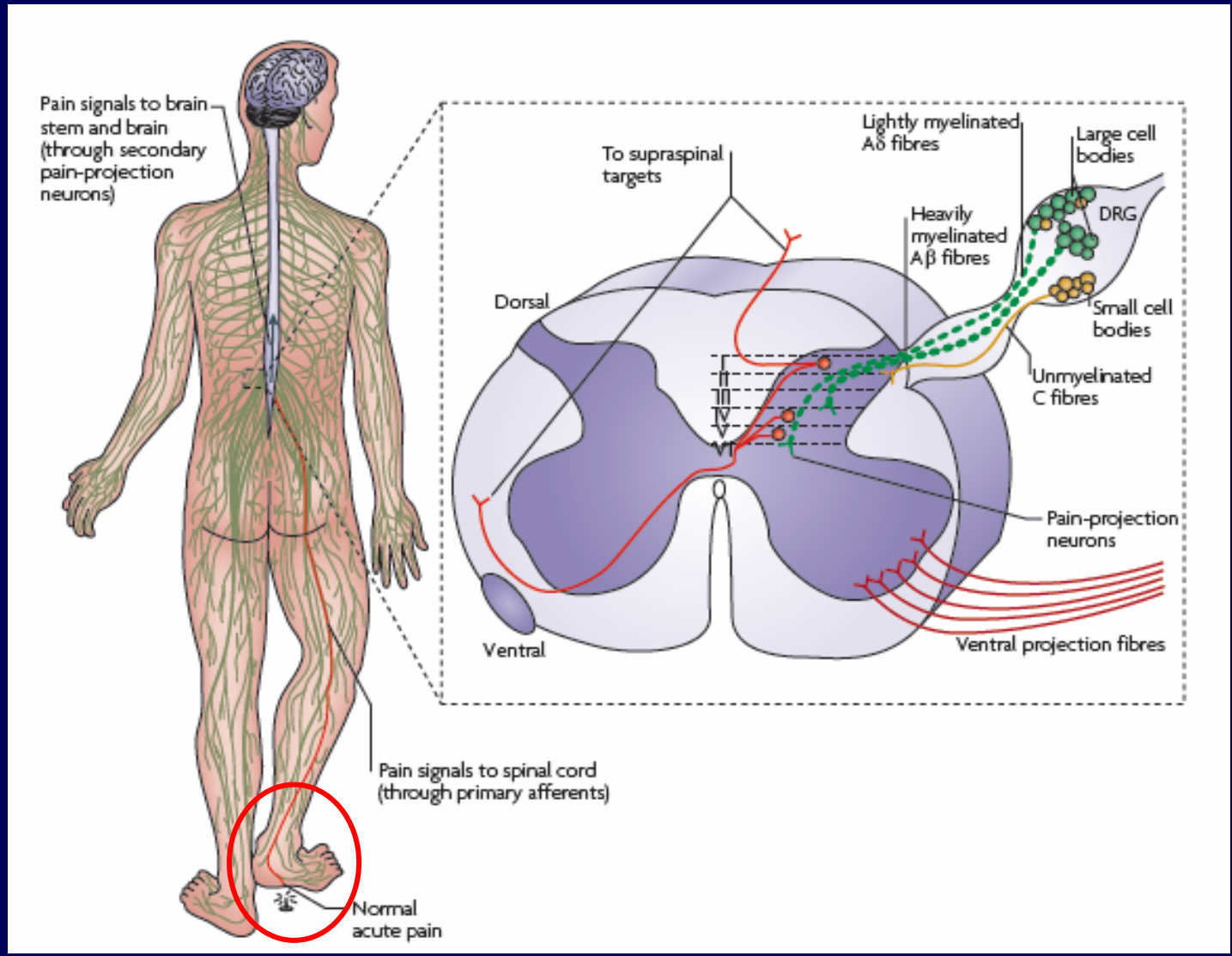
  - *Hipotálamo (IG = 8 sem) – Noradrenalina, 5-HT, dopamina*

  - *Hipófise (IG = 20 sem) – ACTH, endorfinas*

Anand and Hickley. N Engl J Med 1987; 317:1321-1329.

Mecanismos de Transmissão da dor

Neuroanatomia básica



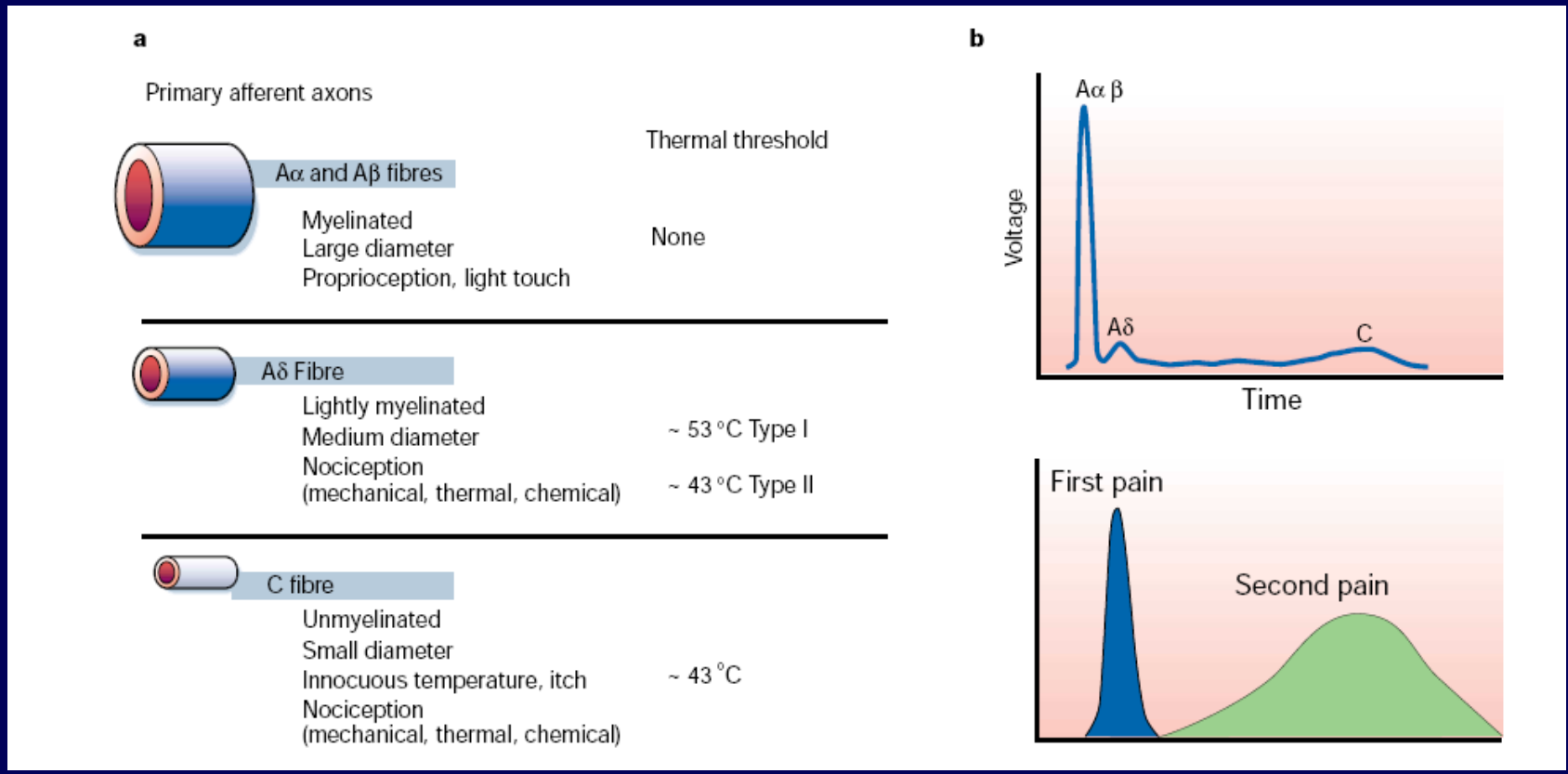
Milligan and Watkins, Nat Rev 2009; 10:23-36.

Mecanismos Periféricos de Transmissão da dor

- Nociceptores
  - Mecanoceptores
  - Termoceptores
  - Polimodais (**TVPV – VR1 e TRPA**)
  - **Silentes**
- Vias de transmissão nervosa
  - Fibras A-delta (2-6 mcM, 12-30 m/s) 10%
  - Fibras C (0,4-1,2 mcM, 0,5-2 m/s) 70%
  - **Fibras A-beta** (>10 mcM, 30-100 m/s) 20%

Stucky et al., PNAS 2001; 98:21-22.

Mecanismos Periféricos de Transmissão da dor



Julius and Basbaum. Nature 2001; 413:203-10.

Mecanismos Periféricos de Transmissão da dor

Lesão tecidual + liberação de fatores inflamatórios e imunes

↓

Quebra de ácidos graxos de cadeia longa e formação de cininas - BRADICININA

↓

Lesão da membrana celular – Ac Araquidônico – formação de PG, PC, LT, TX, LPX

↓

Diminuição do limiar de excitabilidade dos nociceptores (PGE2)

↓

Liberação de citocinas (IL1, IL6, FNT-alfa) pelos macrófagos

↓

Liberação de selectinas, integrinas, fatores quimiotáticos e NO

↓

Migração de células de defesa e adesão celular ao endotélio

Mecanismos Periféricos de Transmissão da dor

Formação de Radicais Livres e Nitrogênio

↓

Produção celular de Catalases, Colagenases e Esteromelisina - Reparação

↓

Inflamação Neurogênica com liberação de mediadores químicos na periferia

↓

SP, PDGC, neurocinina A – vasodilatação e aumento da permeabilidade vascular

↓

Sensibilização Periférica do Nociceptor

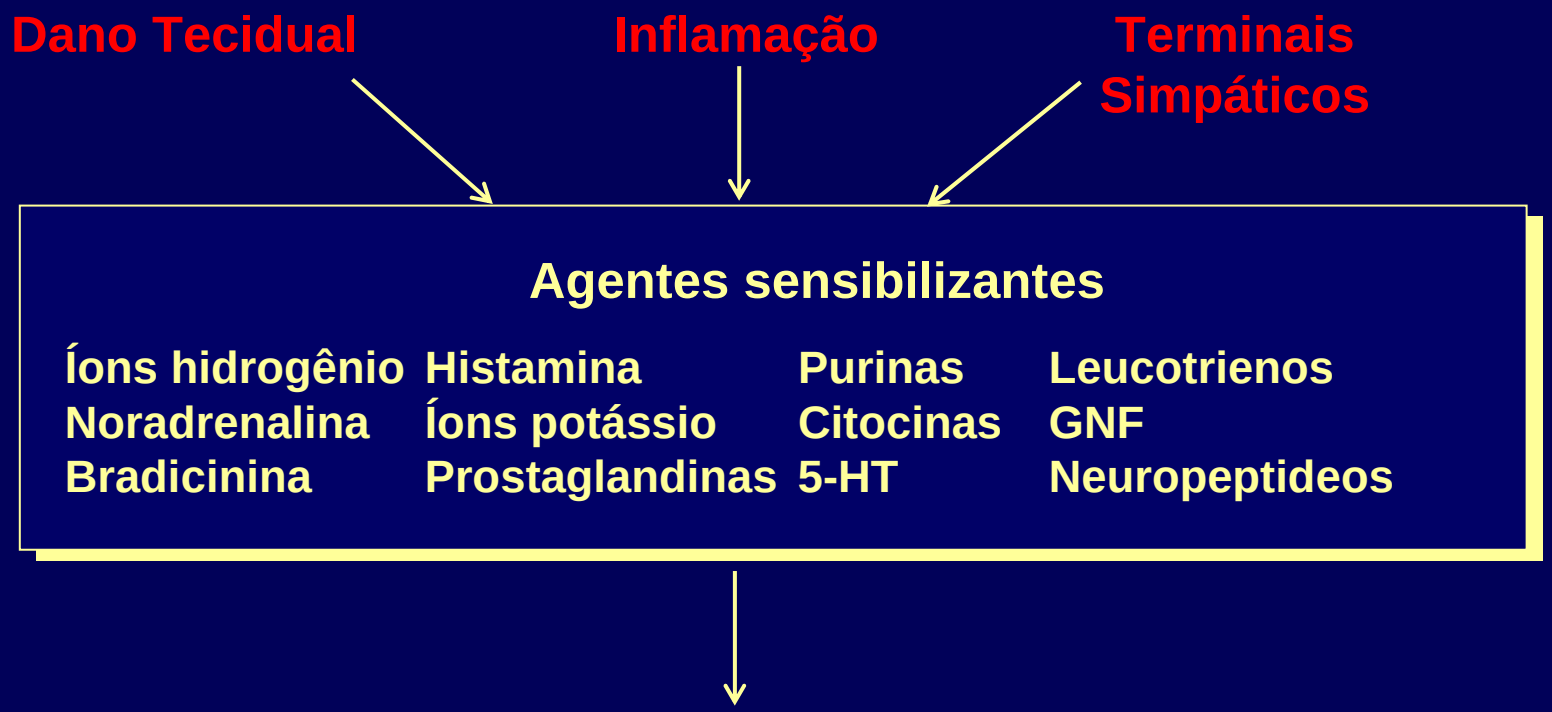
↓

Aumento da expressão de canais de Na e Ca

↓

Transmissão do potencial pelo axônio até a Medula Espinhal

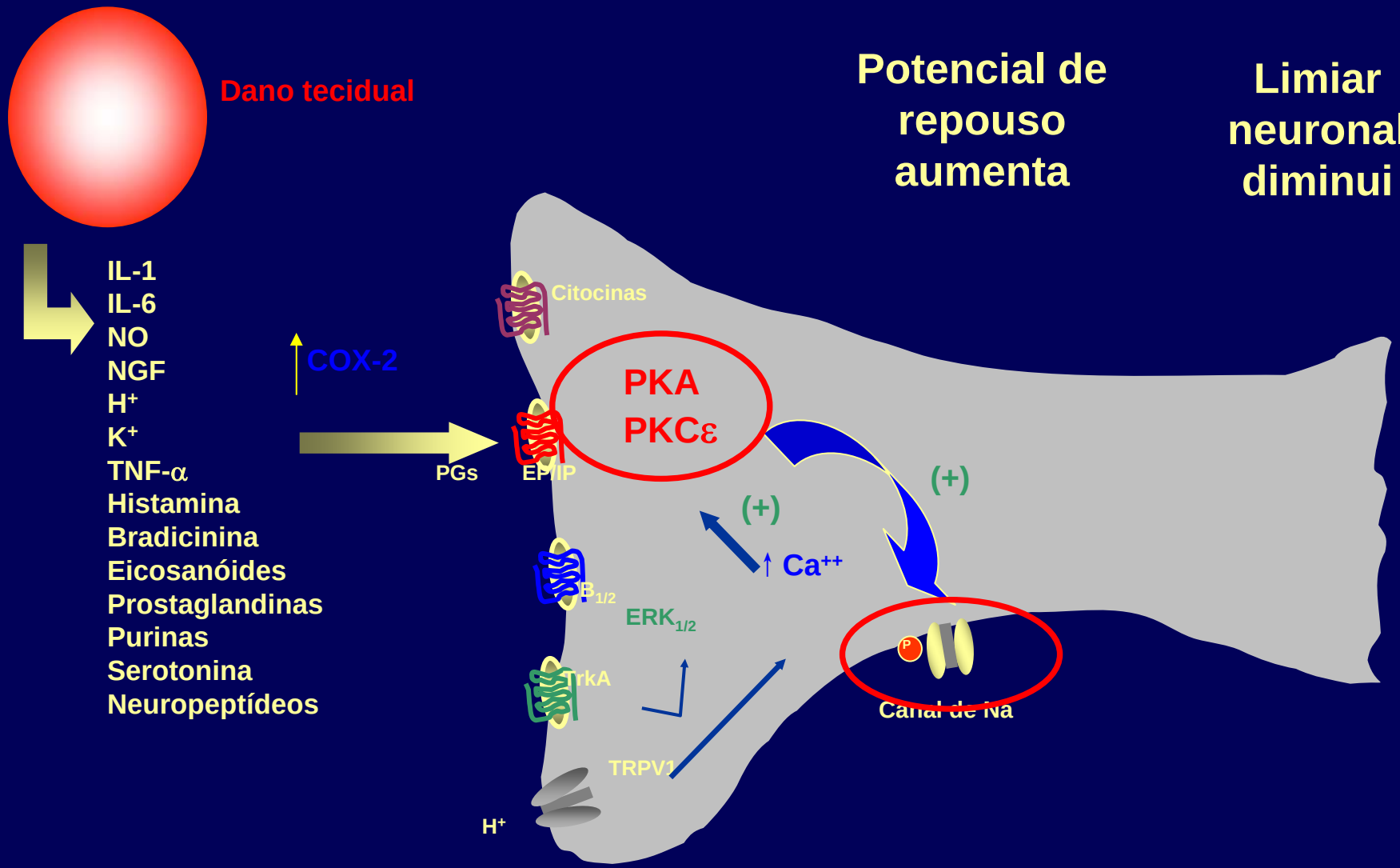
Sensibilização Periférica



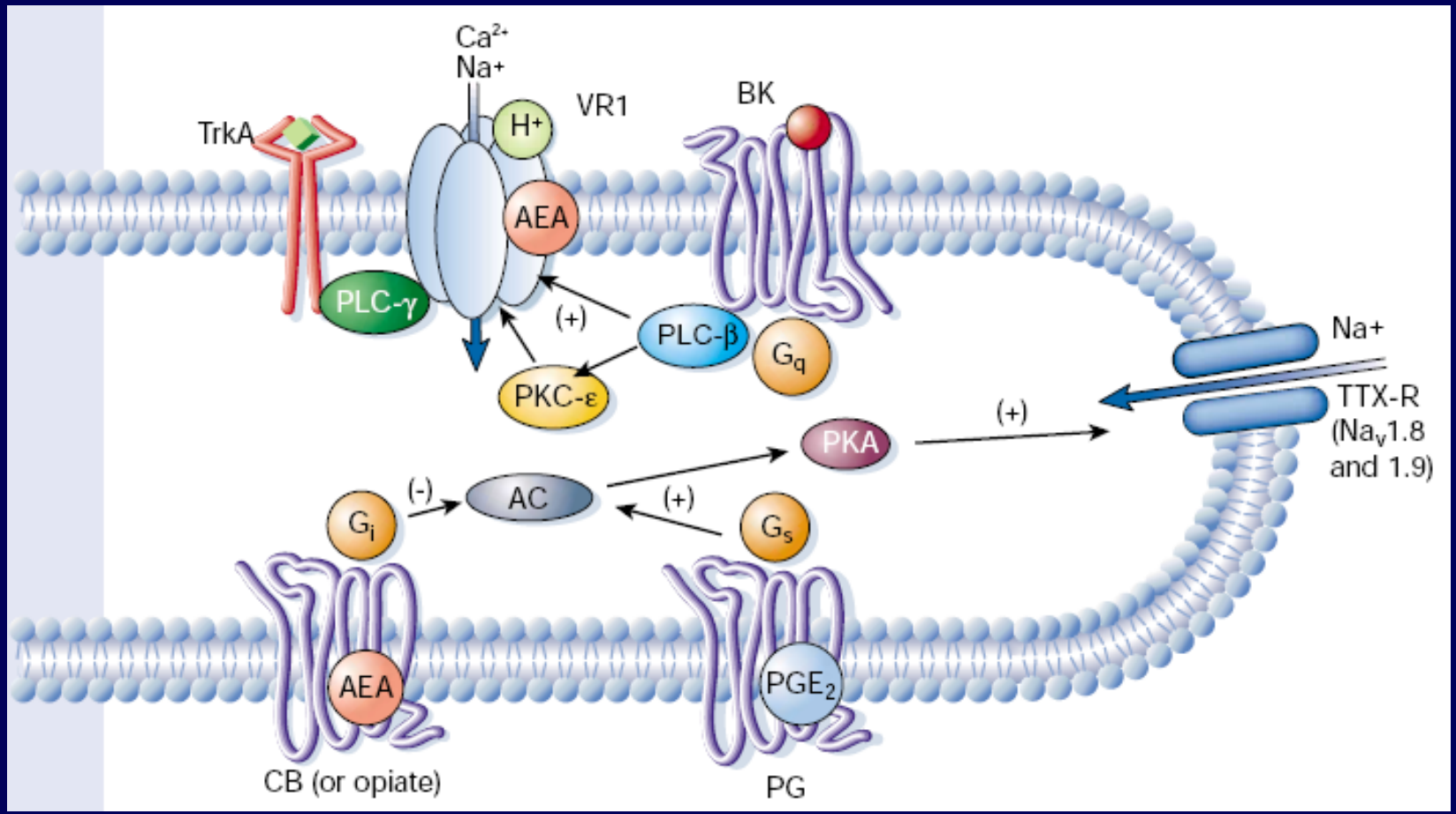
Diminuição do limiar dos nociceptores
Discargas ectópicas
Acúmulo de canais de sódio

Siddal, Cousins. In: Cousins, Bridenbaugh, eds. *Neural Blockade*. 1998:675-699.

MECANISMOS PERIFÉRICOS DA DOR



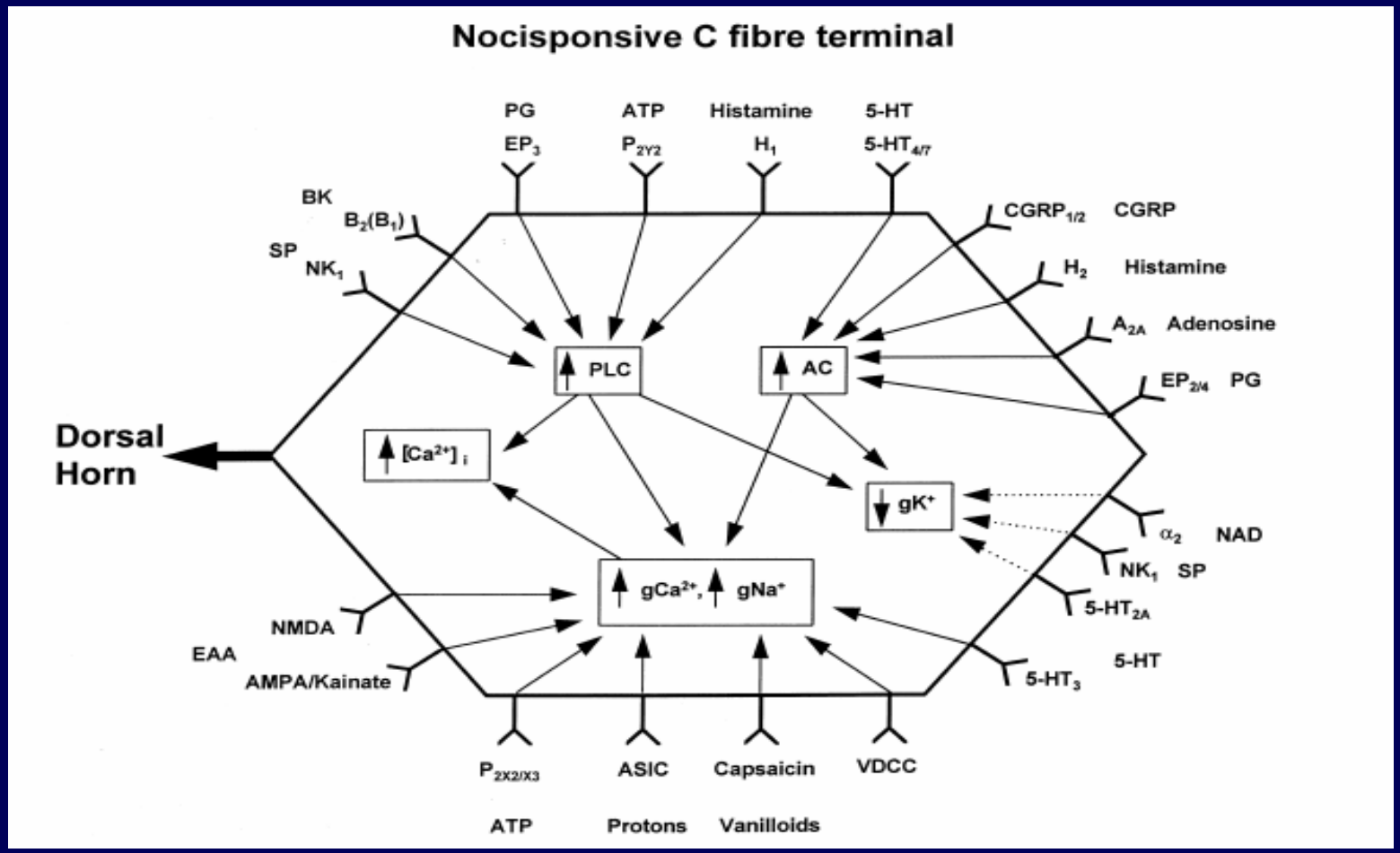
Mecanismos periféricos da dor



Julius and Basbaum. Nature 2001; 413:203-10.

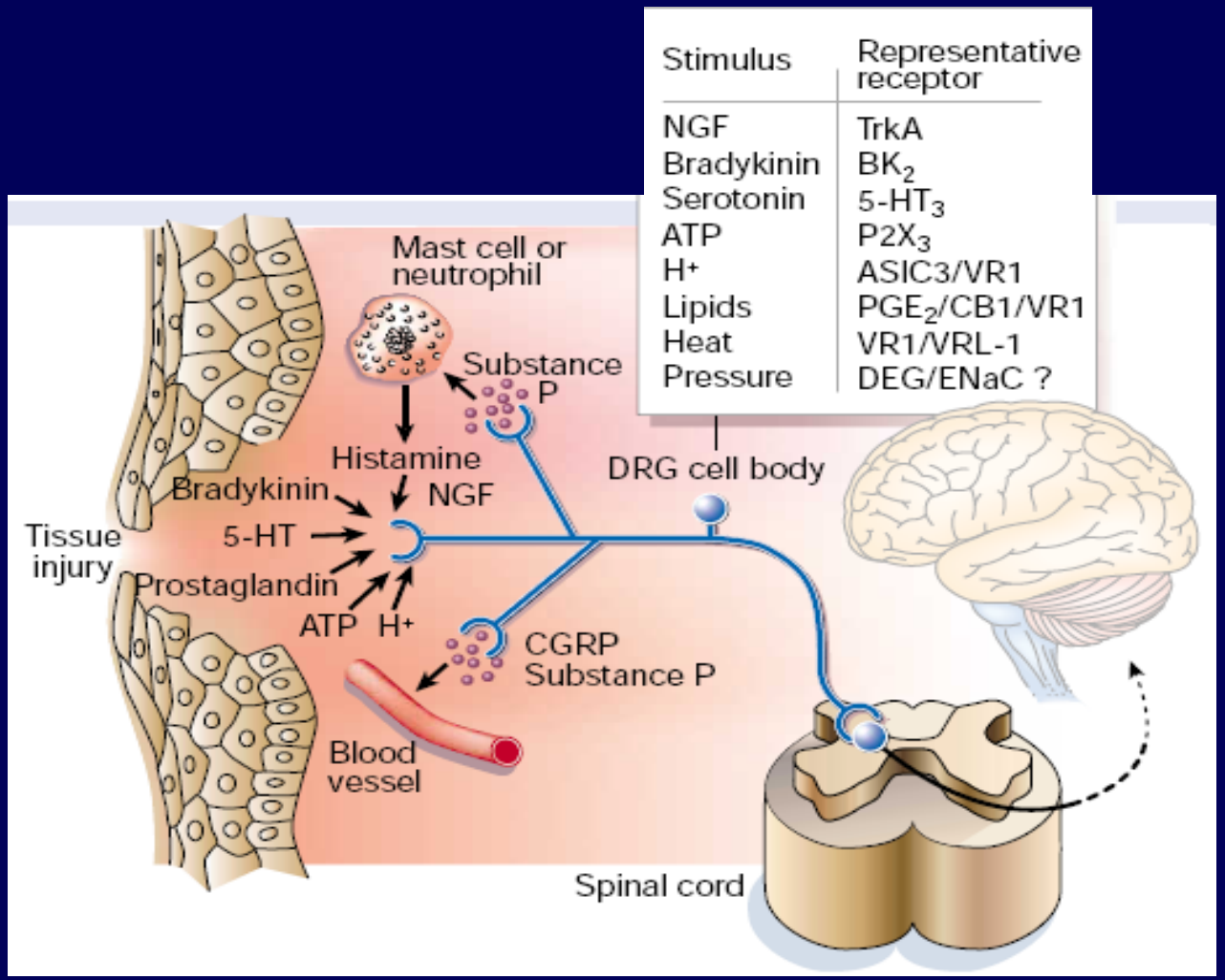
Mecanismos de Transmissão da dor

Terminais em fibras C



Millan MJ, Prog Neurobiol 1999; 57:1-164.

Mecanismos periféricos da dor



Julius and Basbaum. Nature 2001; 413:203-10.

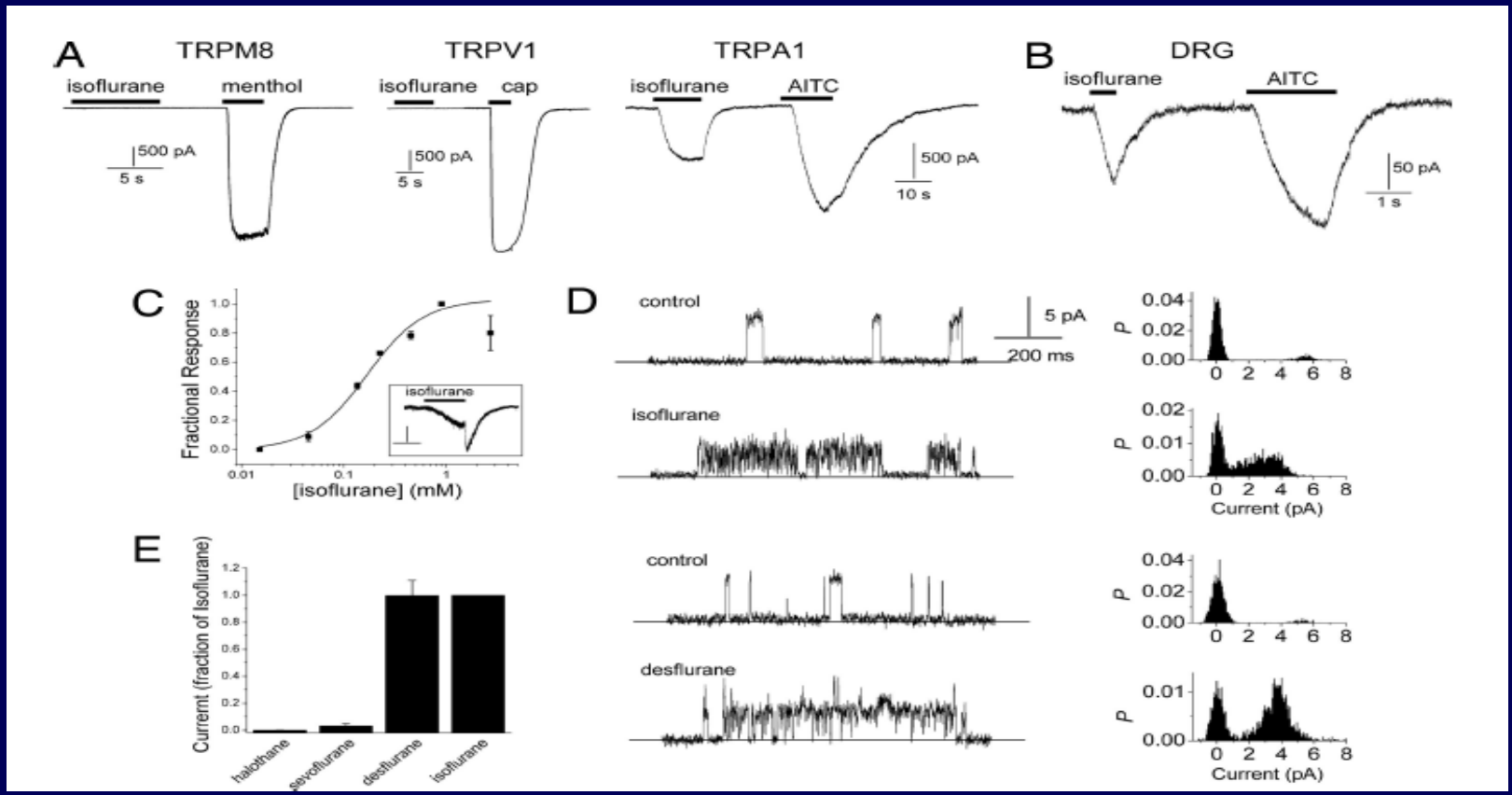
DISCUSSÃO DE ARTIGO

General anesthetics activate a nociceptive ion channel to enhance pain and inflammation

José A. Matta*, Paul M. Cornett*, Rosa L. Miyares*, Ken Abe†, Niaz Sahibzada*, and Gerard P. Ahern*‡

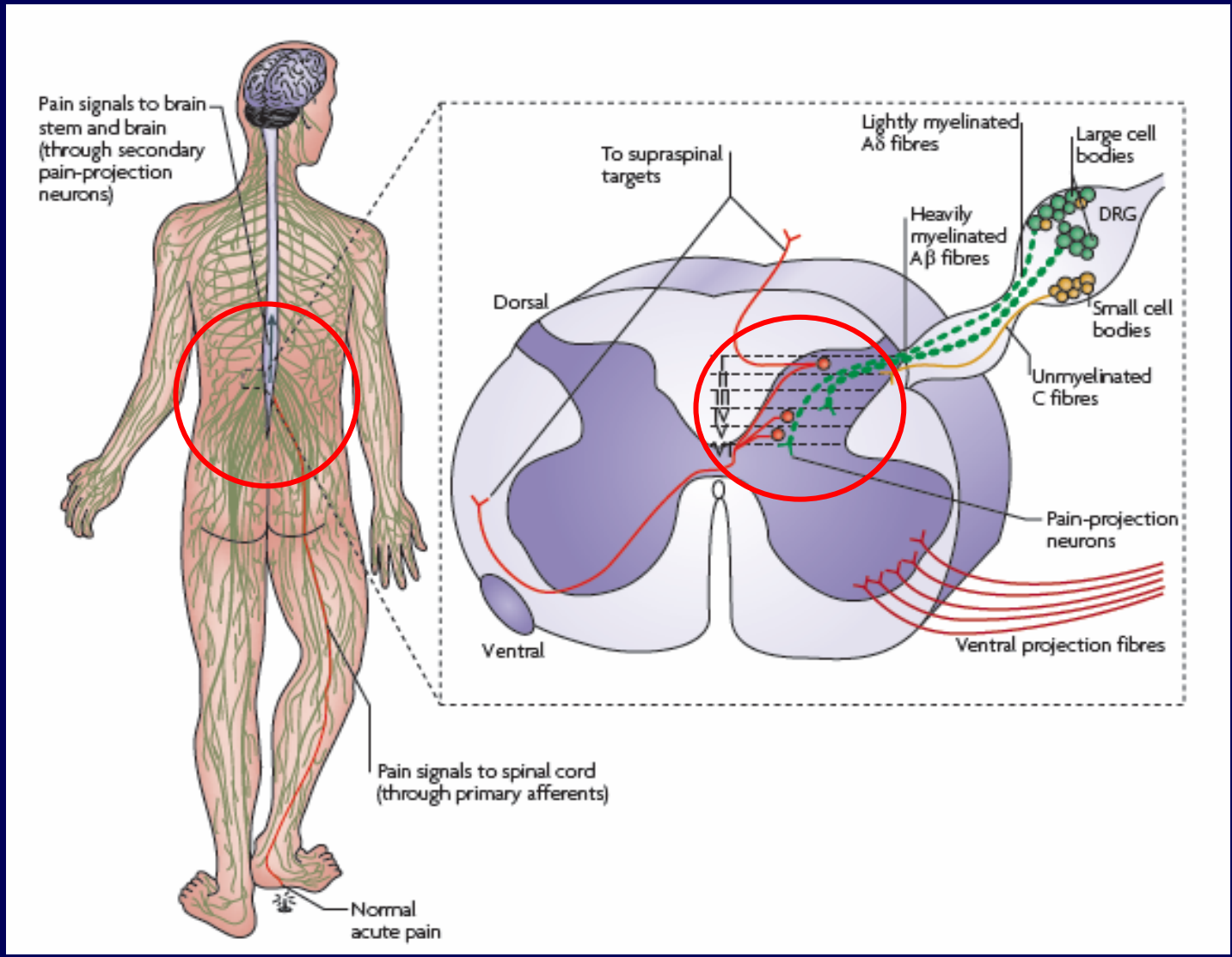
Departments of *Pharmacology and †Physiology and Biophysics, Georgetown University, 3900 Reservoir Road, NW, Washington, DC 20007

8784–8789 | PNAS | June 24, 2008 | vol. 105 | no. 25



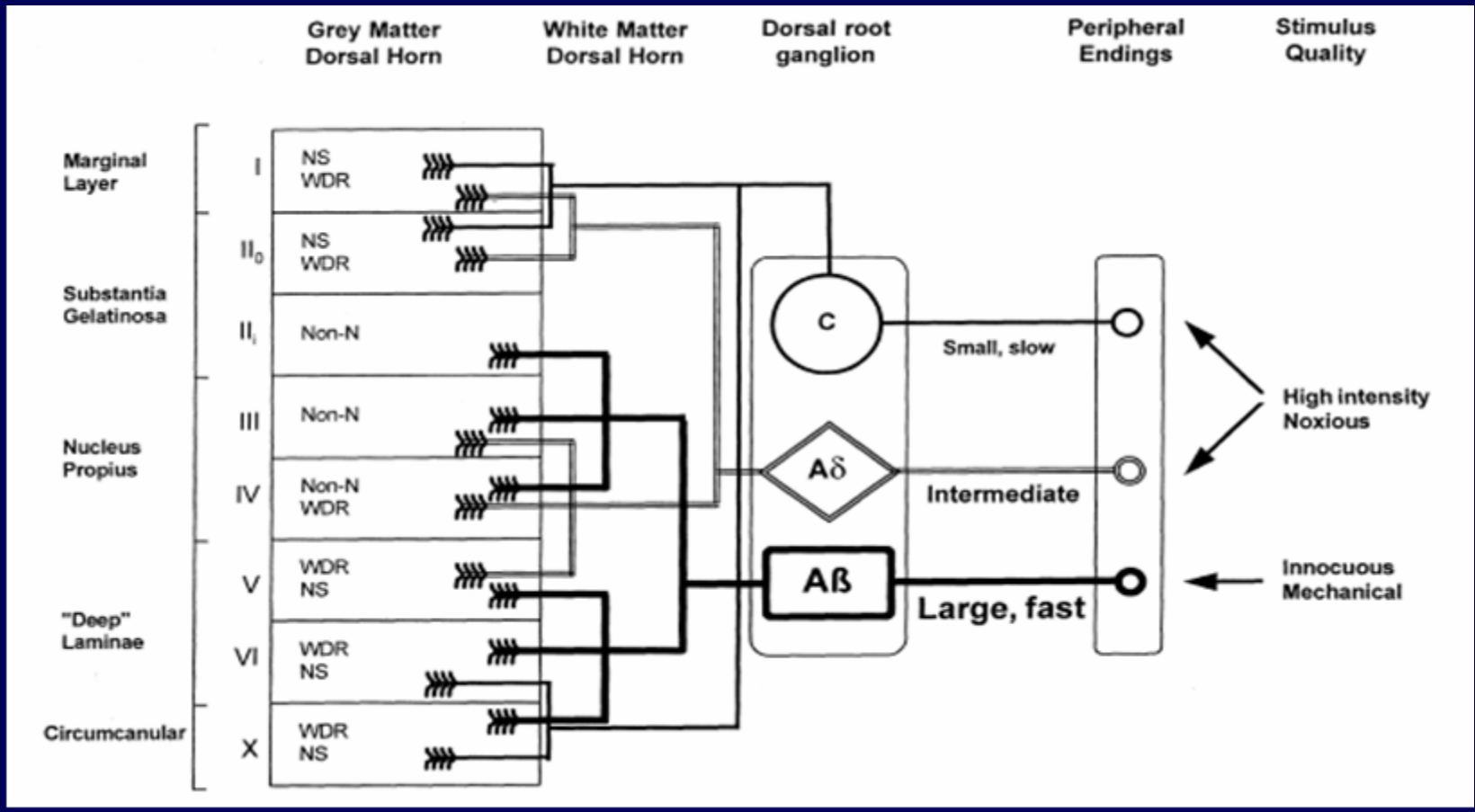
Mecanismos de Transmissão da dor

Neuroanatomia básica



Milligan and Watkins, Nat Rev 2009; 10:23-36.

Mecanismos de Transmissão da dor



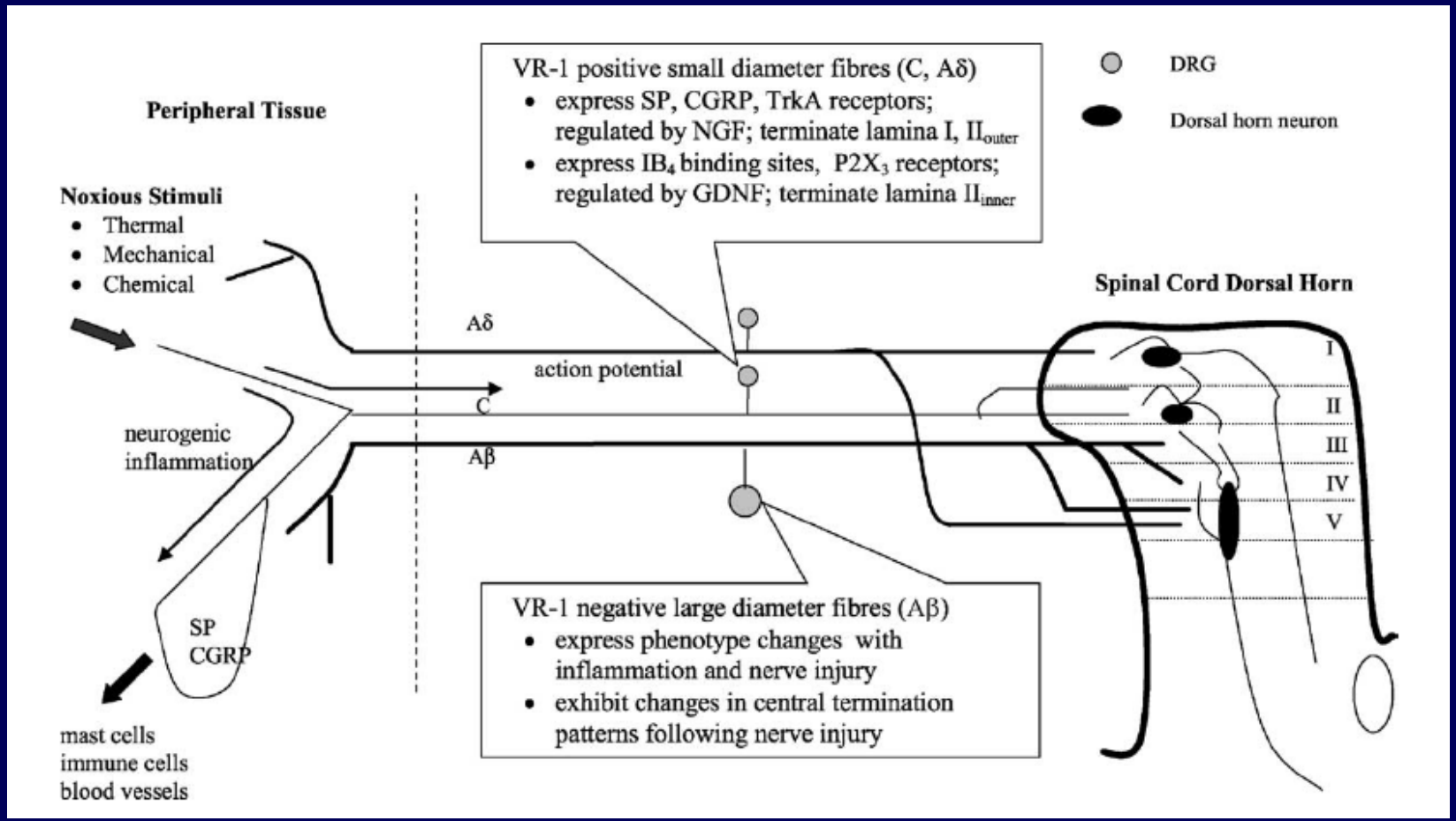
Millan MJ, Prog Neurobiol 1999; 57:1-164.

Mecanismos de Transmissão da dor

Fibre class	Threshold for activation	Principal transmitters*	Receptors engaged*	DH Laminae innervated†	Neurone types targeted	Sensation mediated	
						Physiological	Pathological
C	High	SP/NKA CGRP EAA	$NK_{1/2}$ $CGRP_{1/2}$ NMDA/ AMPA mGlu	I/II_0 IV/V, X	NS WDR	Noxious (pain)	Highly noxious (hyperalgesia) Cold allodynia (pain)
Aβ	Low	EAAs	AMPA	III–VI	NON-N WDR	Innocuous (no pain)	Mechanical allodynia (pain)

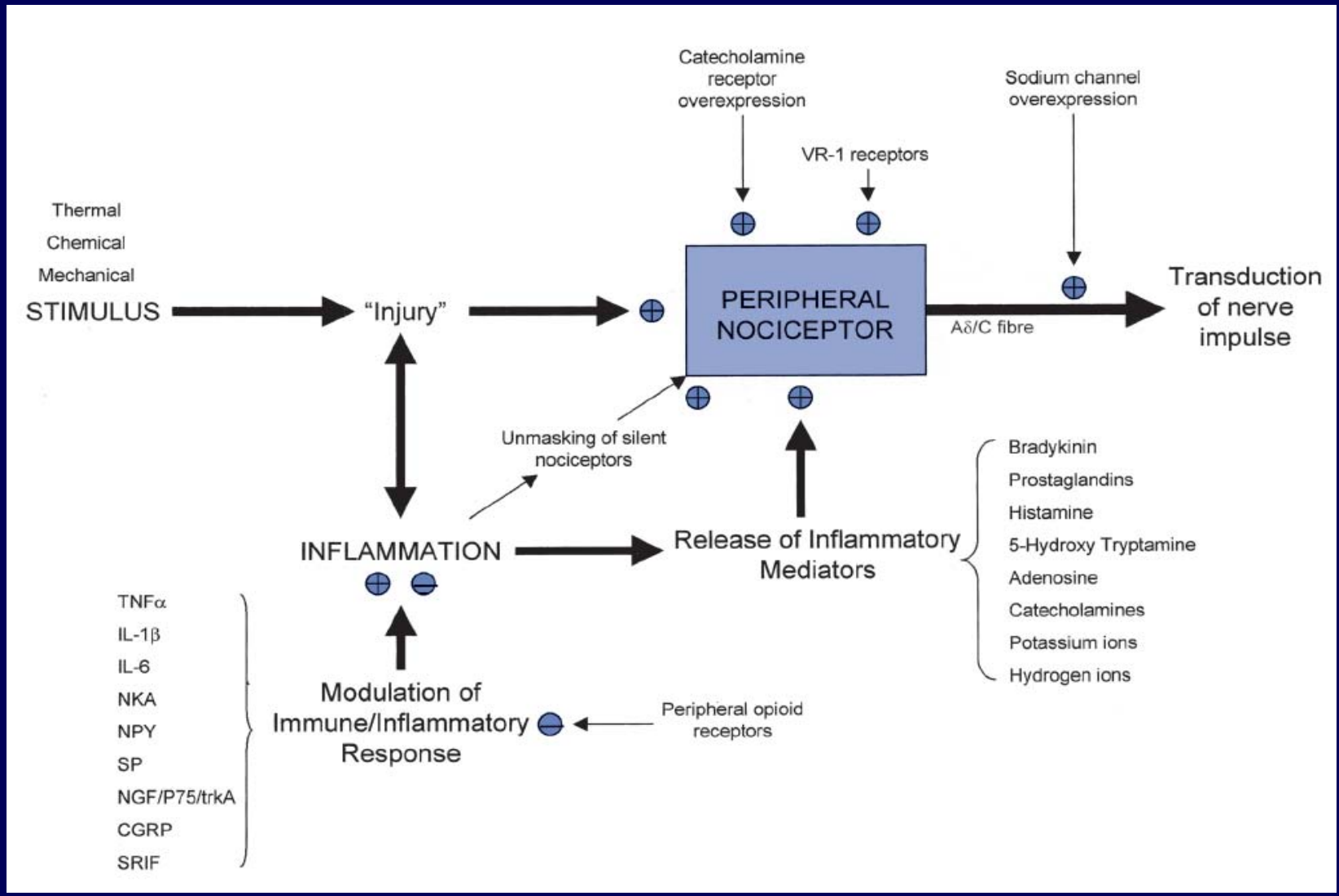
Millan MJ, Prog Neurobiol 1999; 57:1-164.

Mecanismos de Transmissão da dor



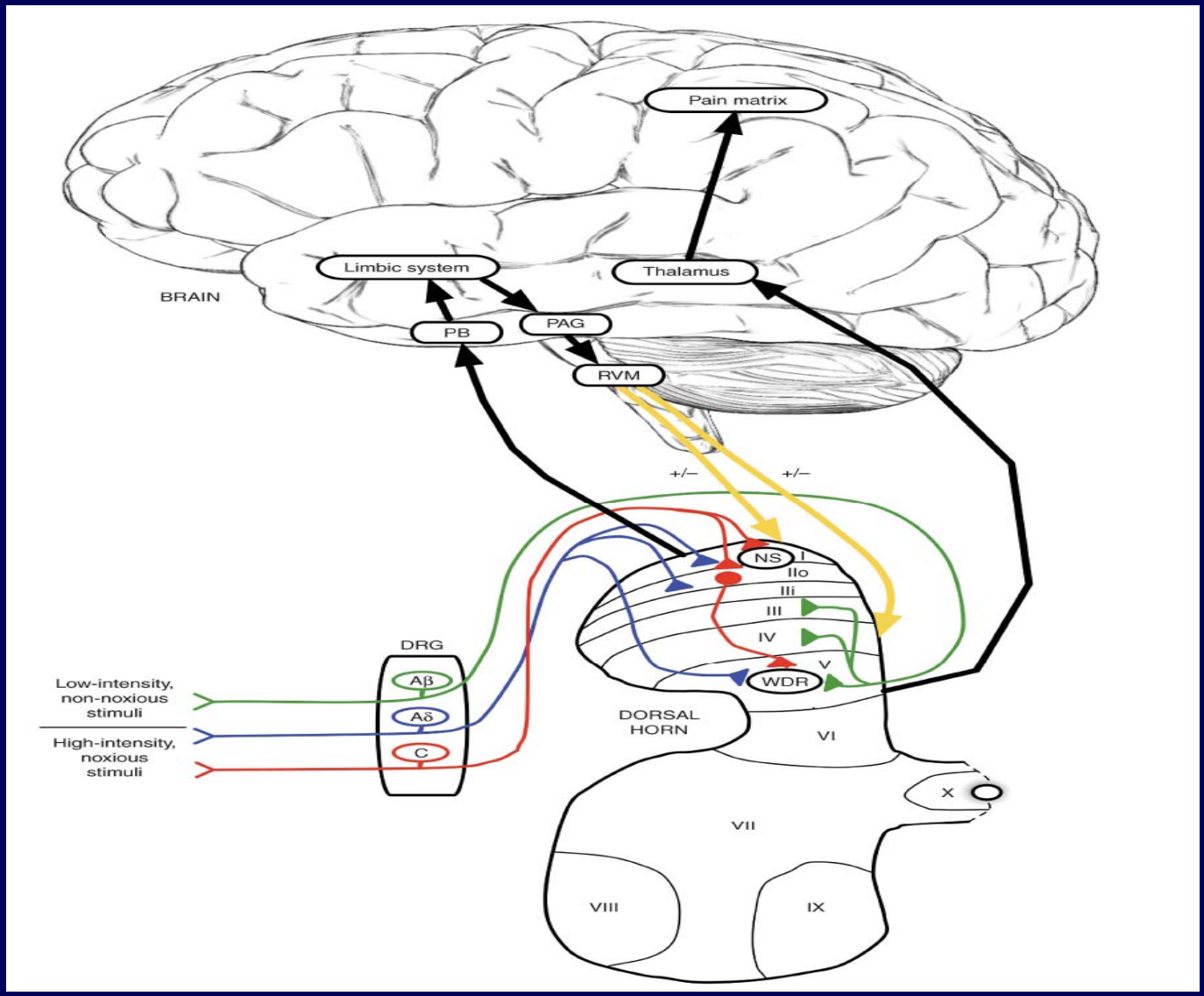
Millan MJ, Prog Neurobiol 1999; 57:1-164.

Mecanismos de Transmissão da dor



Hill RG, The Neuroscientist 2001; 7:282-92.

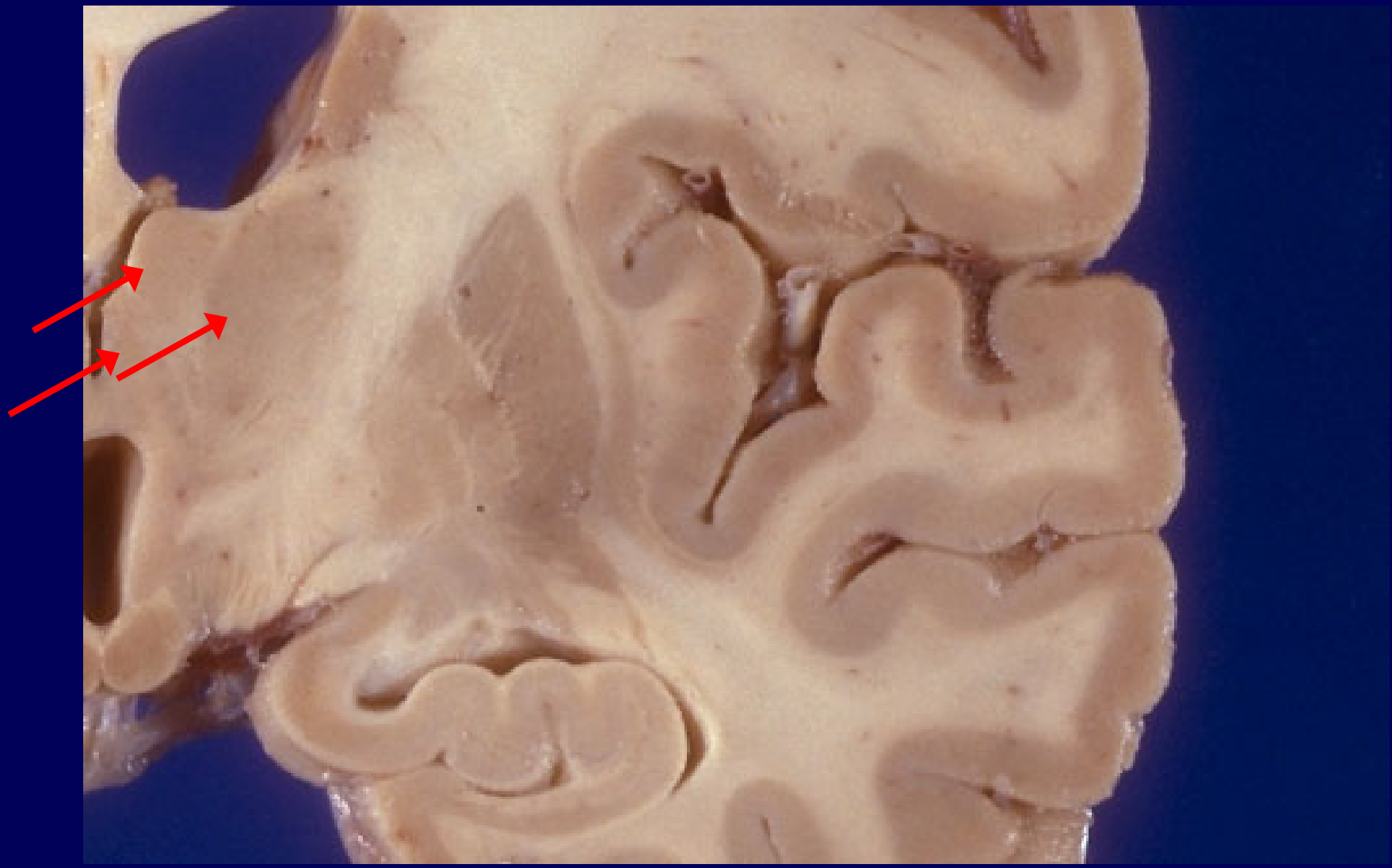
Mecanismos de Transmissão da dor



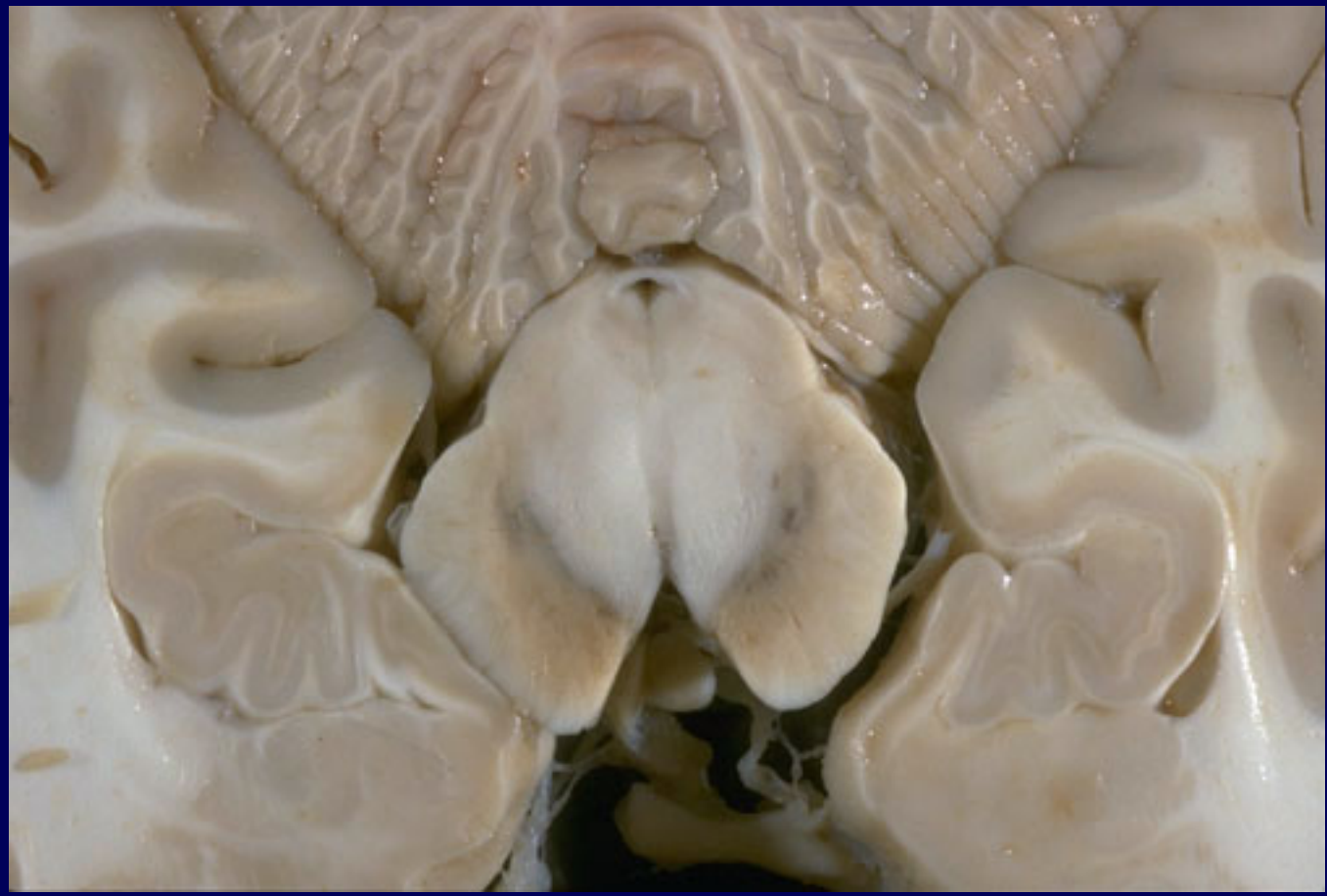
D'Mello and Dickenson, BJA 2008; 101:8-16.

Neuroanatomia da dor

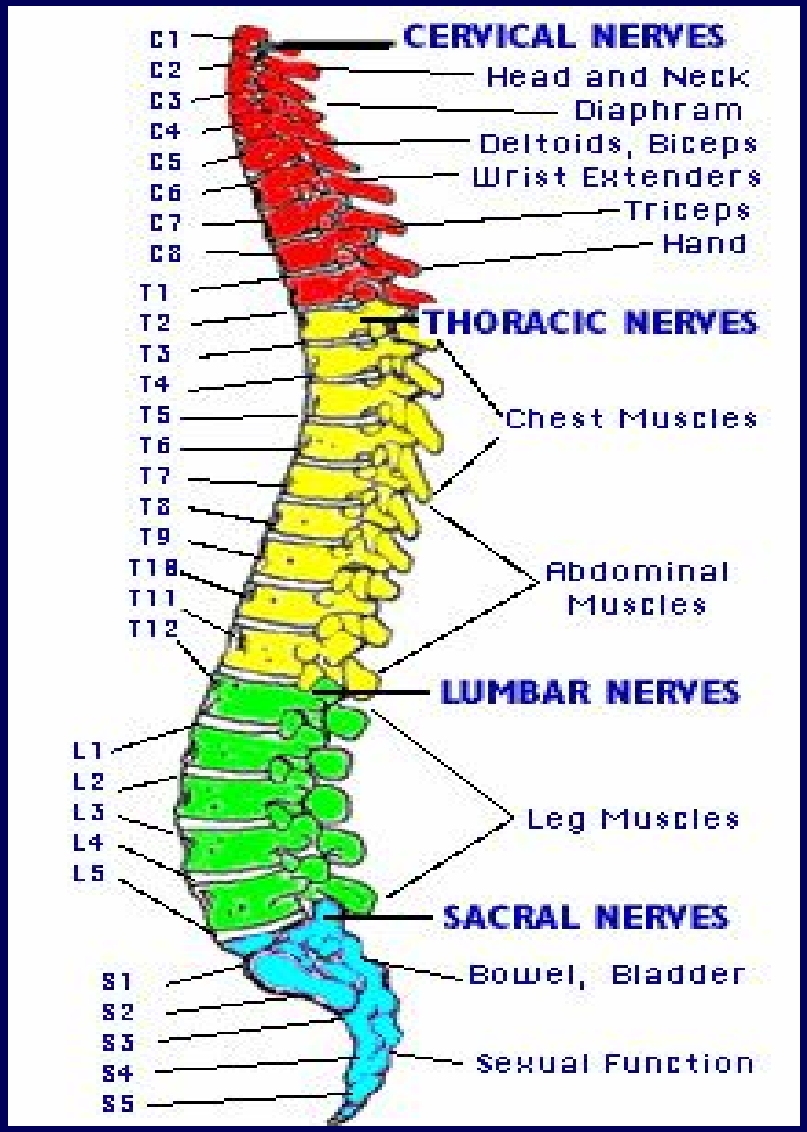
Neuroanatomia da dor

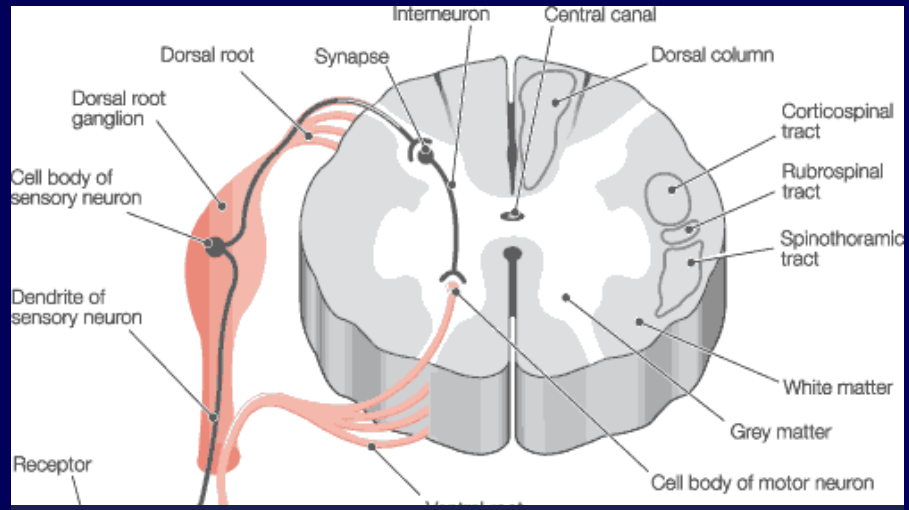


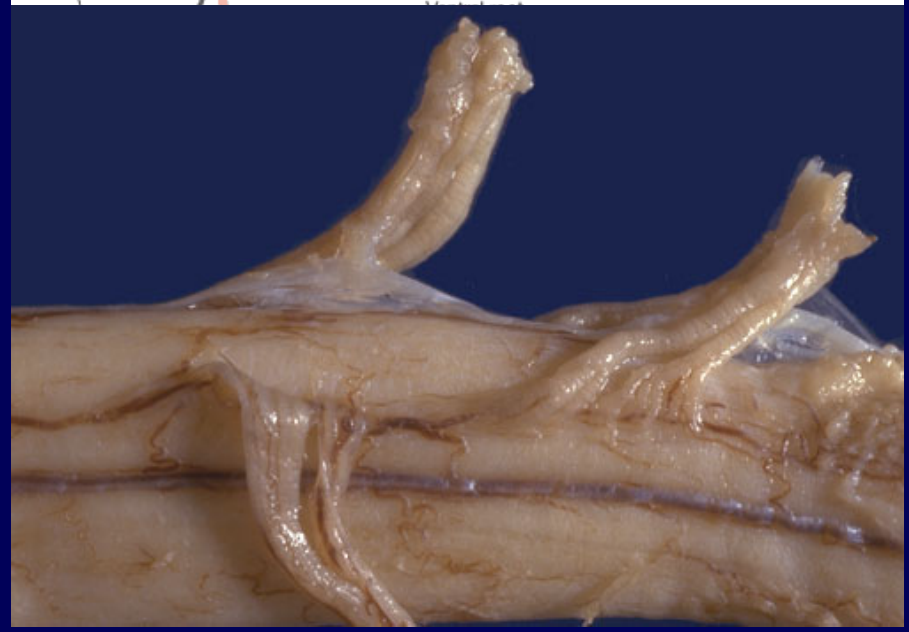
Neuroanatomia da dor



Neuroanatomia da dor







Mecanismos de Transmissão da dor

Vias ascendentes

Tract	Laminae of origin	Cell types	Tissue input	Ascending pathways	Principal sub-cortical targets	Somatic Organization	Axon types	Phylogenetic distribution	Possible roles
Spinothalamic tract	I II (few) IV V/VI VII/VIII LSN	NS WDR Non-N (few)	Skin Viscera Joints/muscle	Mainly VLF DLF (I, LSN) Mainly contralateral	Thalamus: VLF → VPL/VPM DLF → VMPo/VPI/MDvc Also PAG and collaterals →Reticular structures	Yes (I–IV)	Unmyelinated Small and large myelinated	All mammals Prominent in primates	Discriminative-sensory (VLF) Motivational-affective (DLF) Descending inhibition
Spinoreticular tract	I V/VI VII/VIII X (few)	NS (most) WDR Non-N (few)	Skin Viscera Muscle	Mainly VLF Mainly contralateral But ipsilateral (I–V) via dorsal columns to DRN	RF of brainstem → LRN (NPGC/NGC), medial thalamus and DRN (few)	No	Small and large myelinated	All vertebrates	Motivational-affective? Descending inhibition
Spinomesence-phalic tract	I–II IV/V VII X LSN	NS (I) WDR Non-N	Skin Viscera Joints/muscle	Mainly VLF DLF (I, LSN) Mainly contralateral	Midbrain and PAG Deep SCL, NCF and PBN Thalamus (few)	Weak	Unmyelinated Small and large myelinated	All vertebrates	Motivational-affective. Autonomic, motor
Spinoparabrachio-amygdaloid tract	I II (few)	NS	Skin Viscera Joints/muscle	DLF-LF Mainly contralateral	PBN → amygdala and stria terminalis	Yes	Unmyelinated Small, myelinated	Mammals	Motivational-affective. Autonomic
Spinoparabrachio-hypothalamic tract	I II (few)	NS	Skin Viscera Joints/muscle	DLF-LF Mainly contralateral	PBN → hypothalamus (VMH).	No	Unmyelinated Small, myelinated	Mammals	Motivational-affective. Endocrine
Spinohypothalamic (spinotelencephalic) tract	I V X LSN	NS WDR Non-N (few)	Skin Viscera	VLF Mainly contralateral	Hypothalamus and thalamus. Also pons, amygdala, striatum (bilateral)	?	Unmyelinated Small, myelinated	Mammals	Sleep, autonomic and endocrine function Thermoregulation
Spinocervical tract	I (few) III/IV (most) V	WDR Non-N (most)	Skin Joints/muscle	DLF Ipsilateral—then contralateral (from LCN)	Relay LCN (CI–C3 level) →Contralateral thalamus (VPL/VMPo) and midbrain (PAG and SCL) Some LCN cells → spinal cord	Cats and monkeys Not rats	Small and large myelinated	All vertebrates Prominent in carnivores and primates	Discriminative-sensory Motivational affective Autonomic?
Postsynaptic dorsal column (ML) pathway	III–V (most) VI VII	NS WDR Non-N	Skin Viscera Joints/muscle	DF (and DLF) Ipsilateral—then contralateral (from DCN)	Relay DCN of caudate medulla: via ML → contralateral thalamus (VPL/VMPo) Also SCL and spinal cord (few)	Yes (VPL)	Small and medium myelinated	Not fish Prominent in mammals	Discriminative-sensory (VPL) Motivational-affective (VMPo)

Millan MJ, Prog Neurobiol 1999; 57:1-164.

Mecanismos de Transmissão da dor

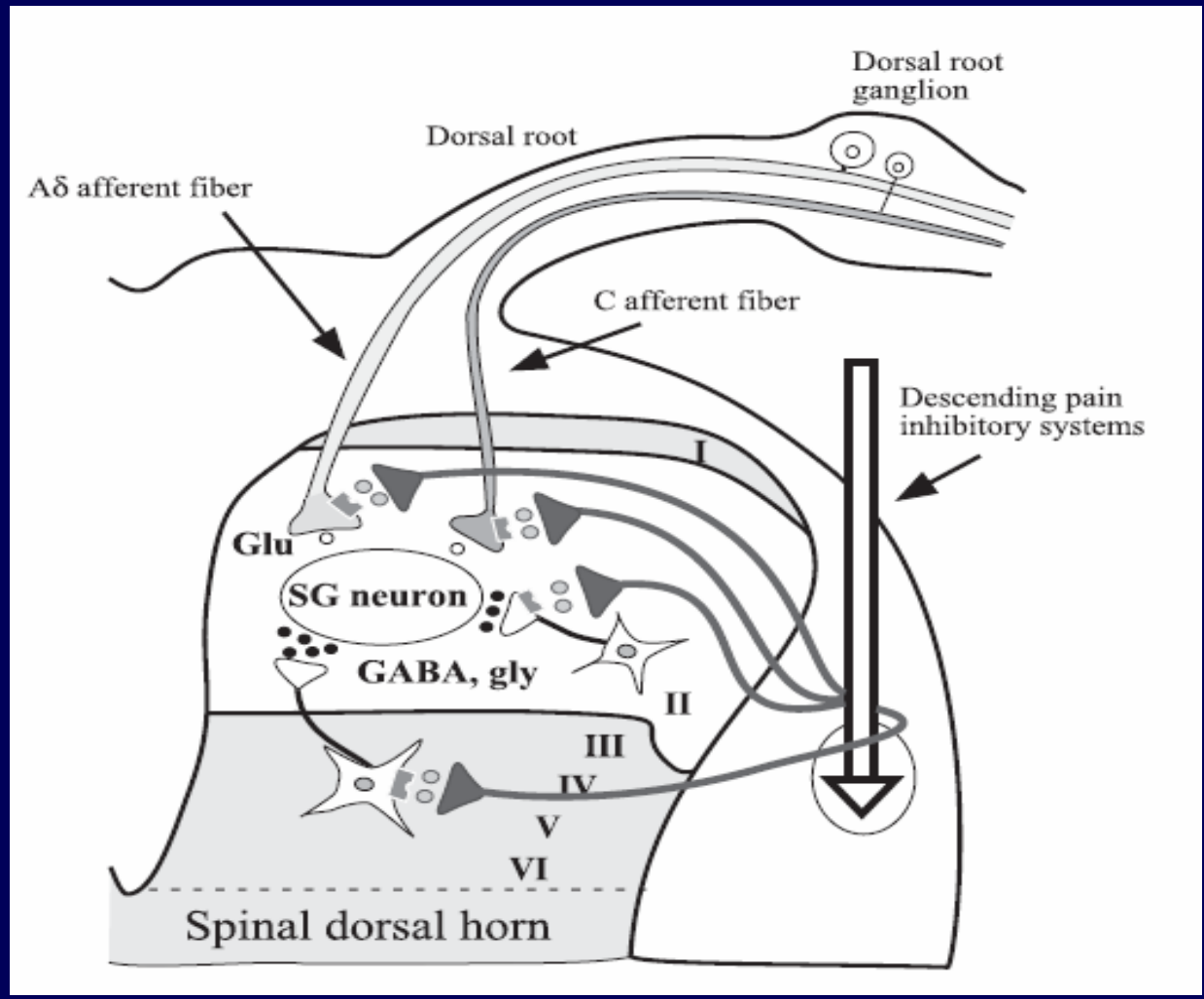
Vias descendentes

- Córtex Cerebral
  - Cingulado Anterior
  - Córtex frontal
  - Córtex parietal
- Hipotálamo
- Subst. Cinzenta Periaquedutal
- Núcleo parabraquial
- NTS
- Medula Ventromedial (N. da Rafe)
- Locus Coeruleus

Yoshimura and Furue. J Pharmacol Sci 2006; 101: 107-17.

Mecanismos de Transmissão da dor

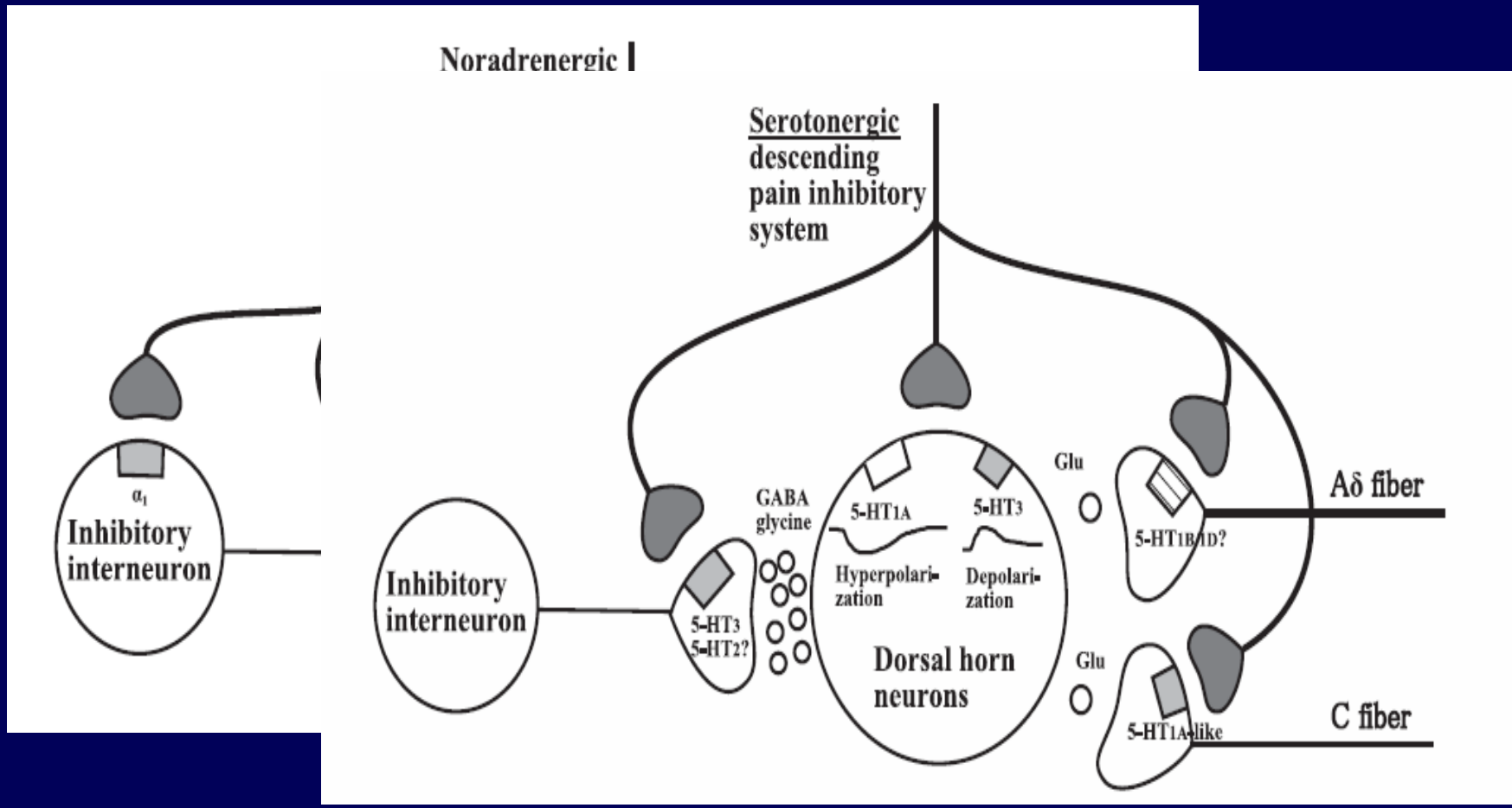
Vias descendentes



Yoshimura and Furue. J Pharmacol Sci 2006; 101: 107-17.

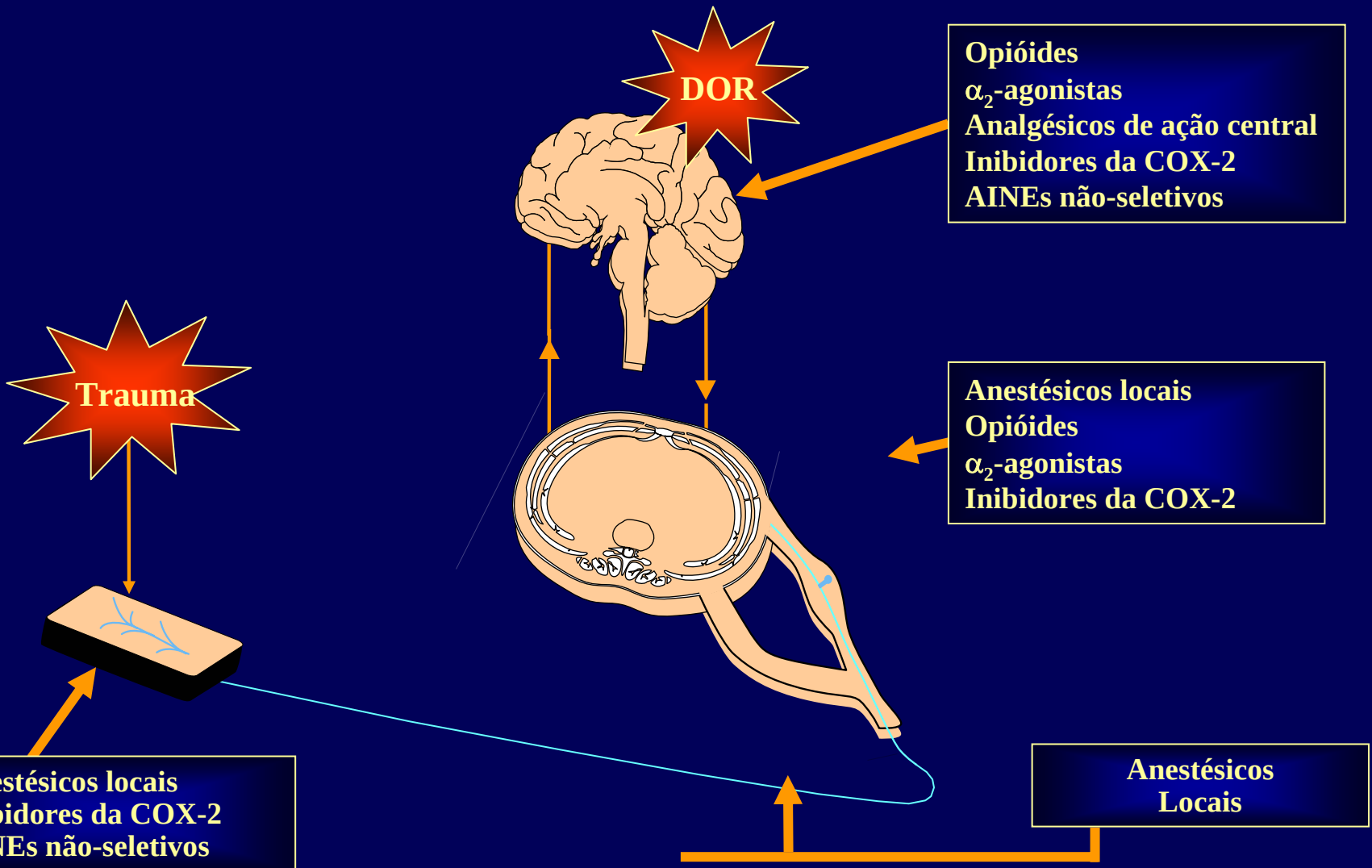
Mecanismos de Transmissão da dor

Vias descendentes



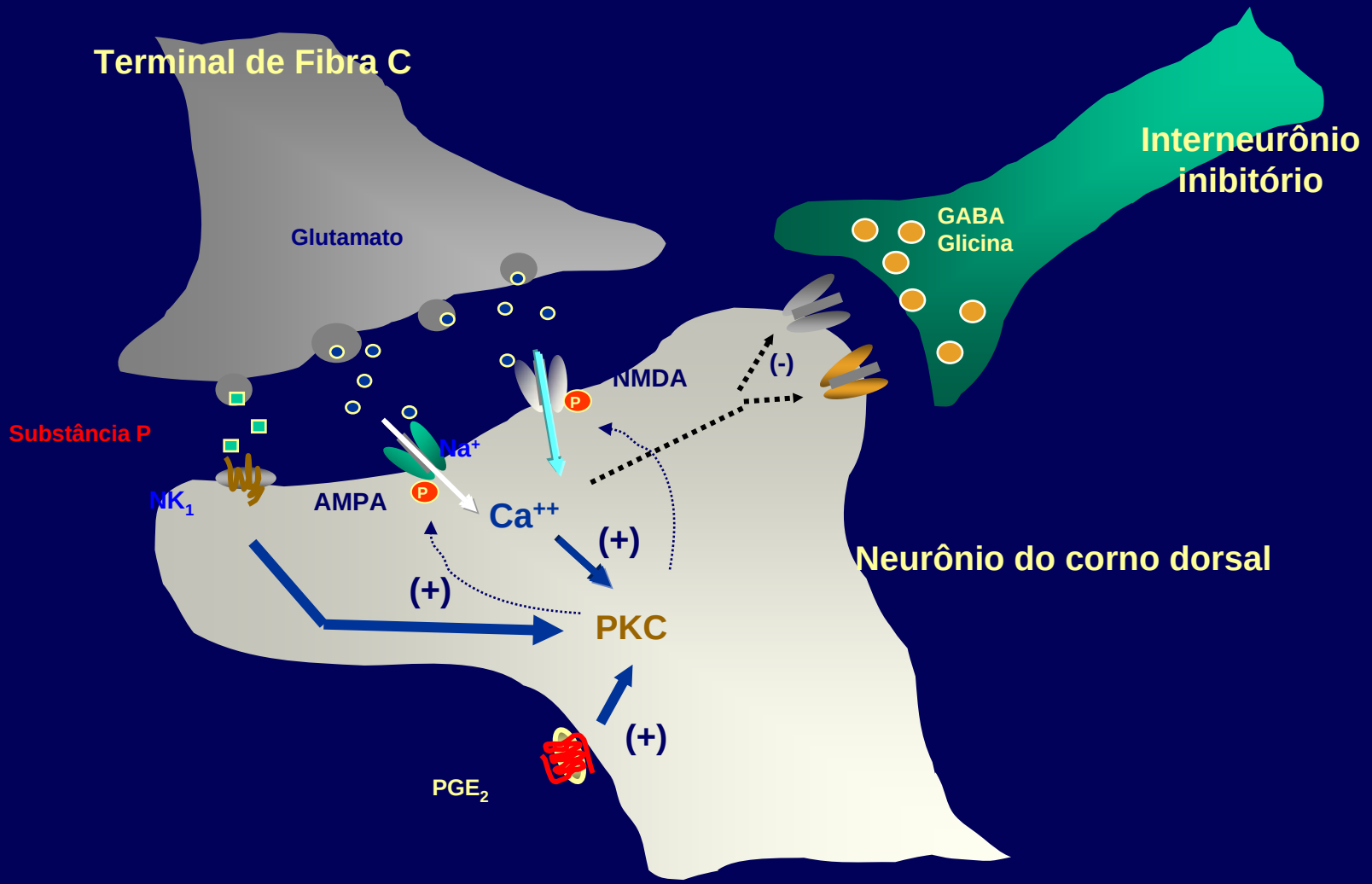
Yoshimura and Furue. J Pharmacol Sci 2006; 101: 107-17.

Analgesia e a transmissão dolorosa

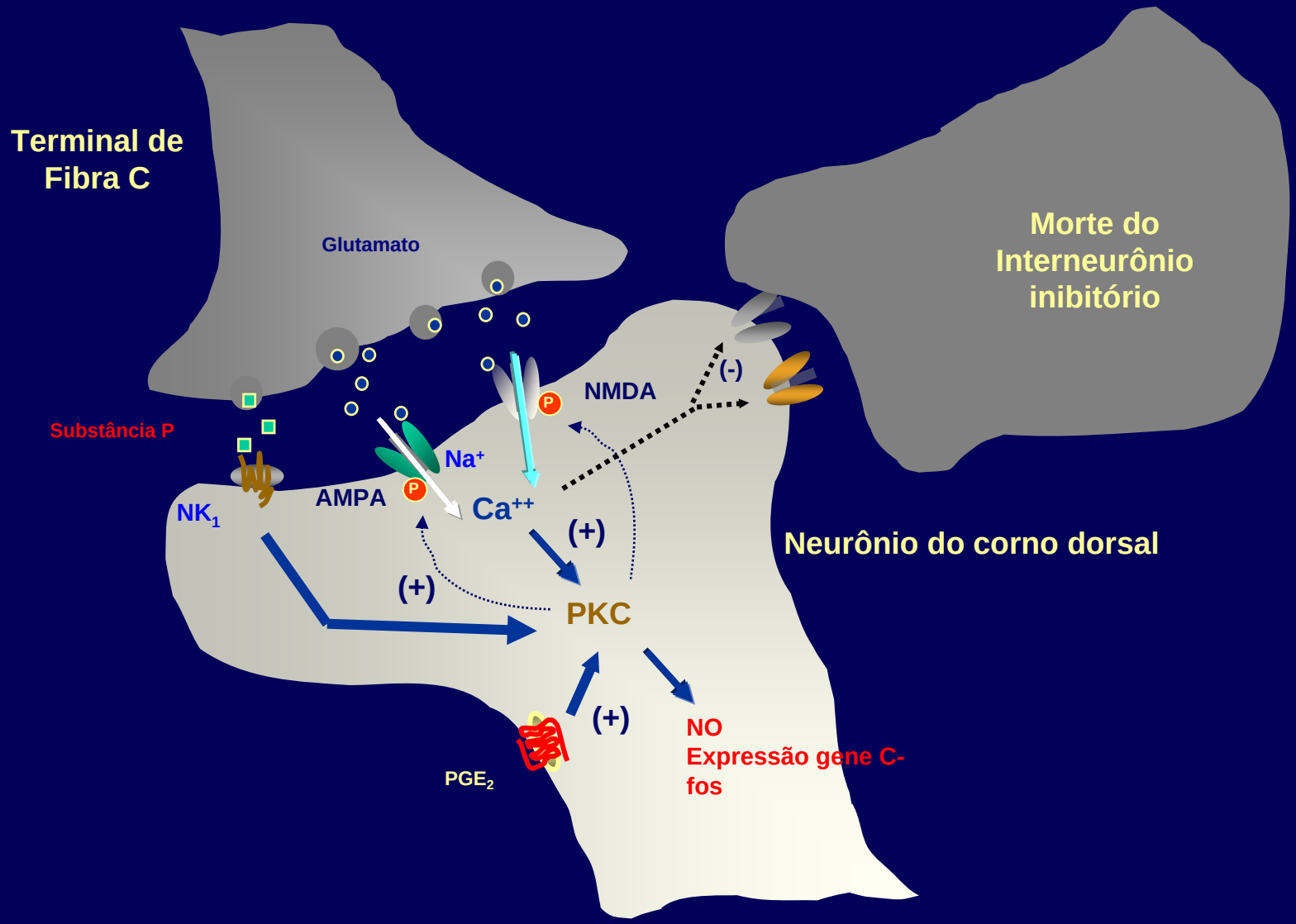


Gottschalk A, Smith DS. *Am Fam Physician*. 2001;63:1979-84.

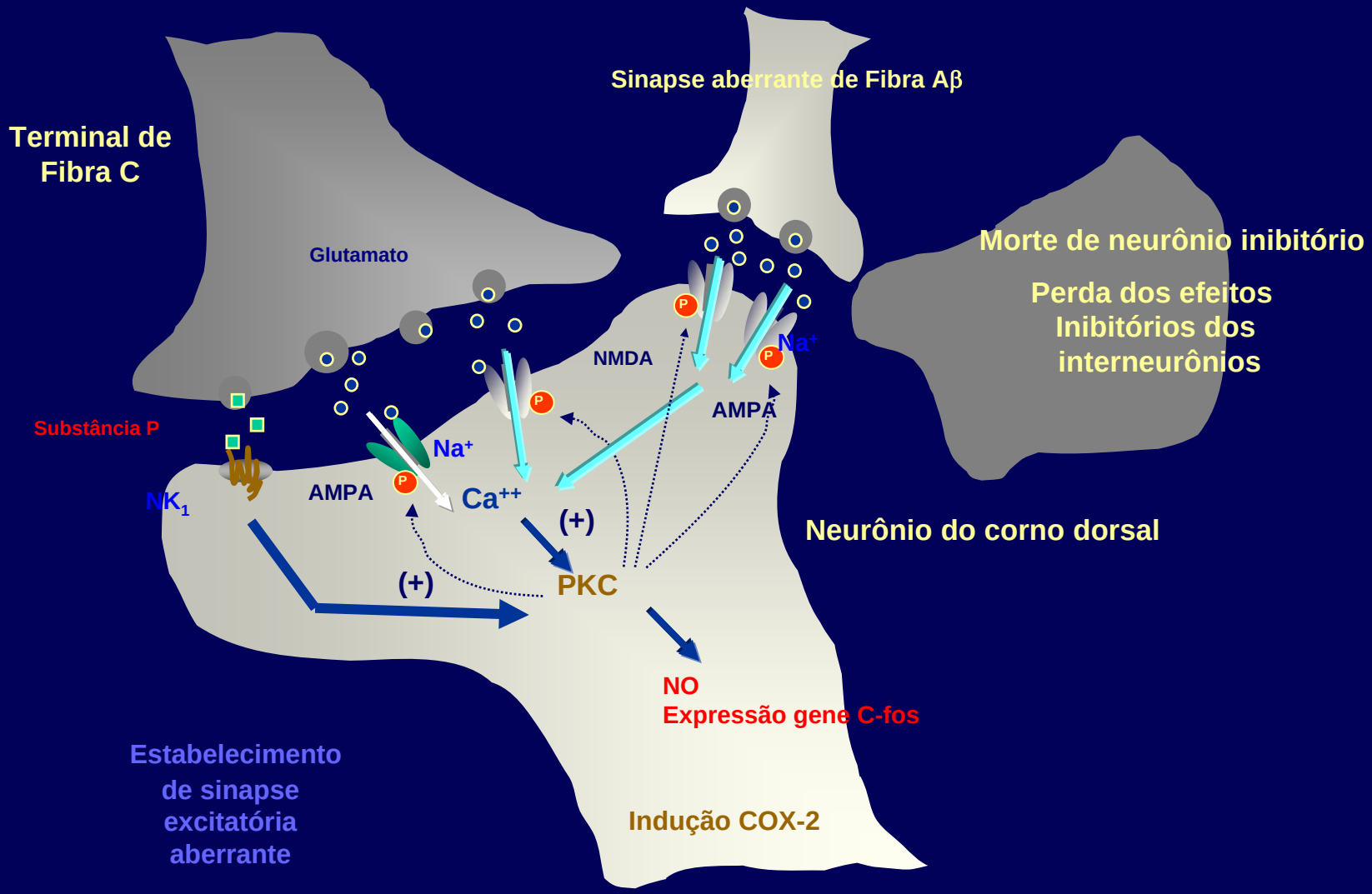
PROCESSAMENTO CENTRAL DA DOR



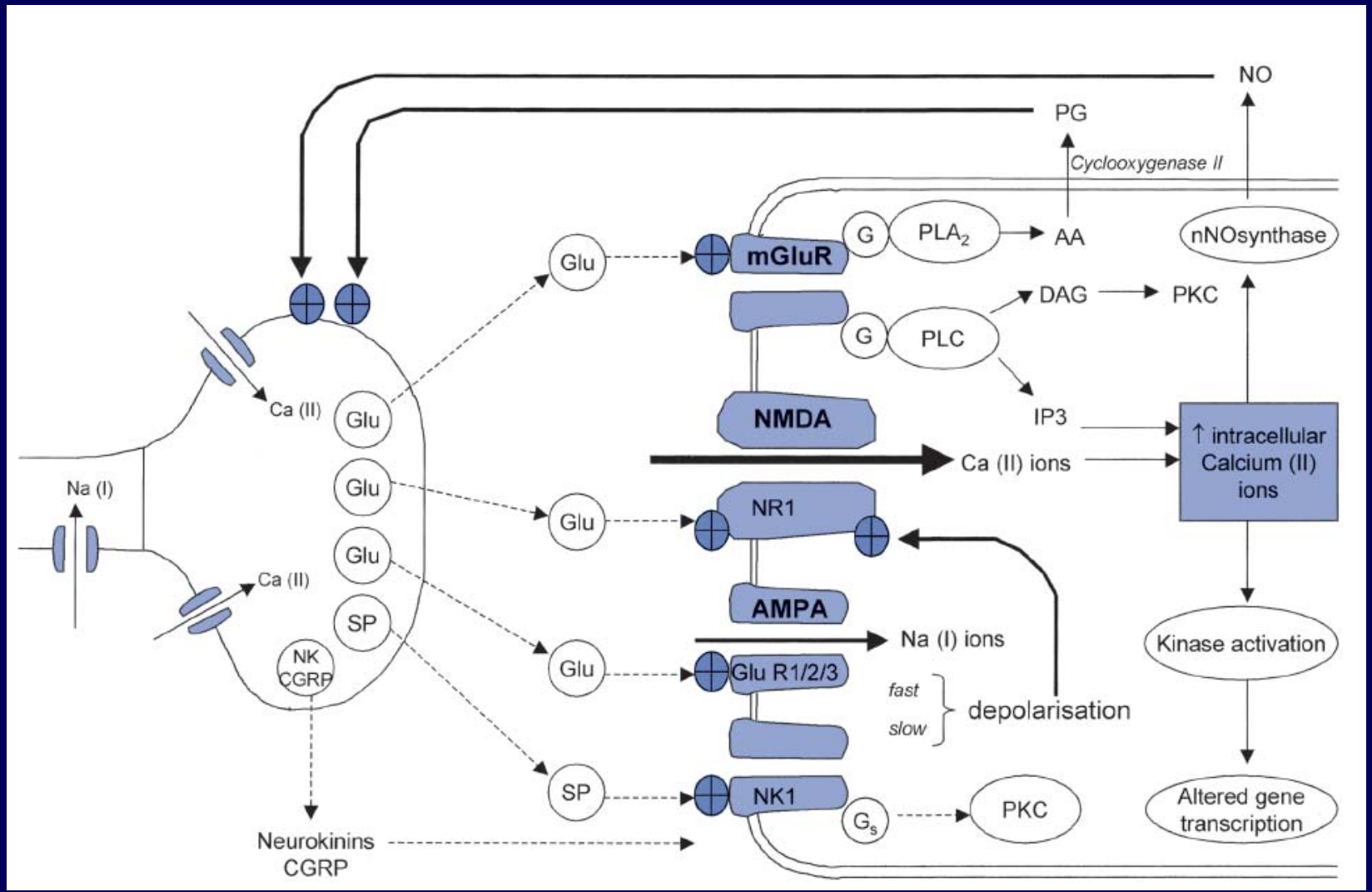
PROCESSAMENTO CENTRAL DA DOR



PROCESSAMENTO CENTRAL DA DOR



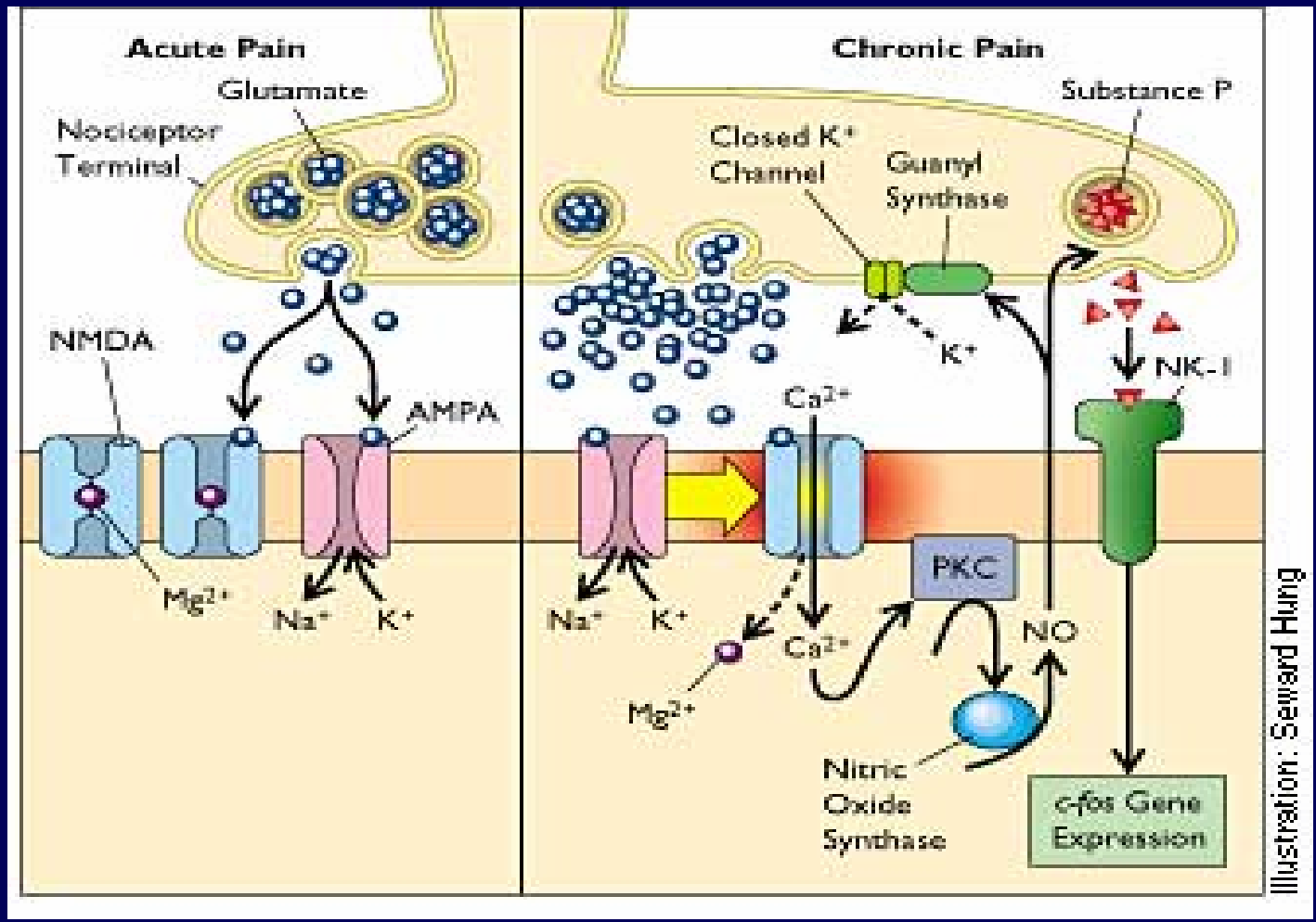
PROCESSAMENTO CENTRAL DA DOR



Hill RG, The Neuroscientist 2001; 7:282-92.

Mecanismos de Transmissão da dor

Sensibilização Central – Receptor NMDA



Ikonomidou et al, Lancet Neurol 2002; 1:383-6.

Sistema Glutamatérgico e Dor

- AA excitatório:
  - Plasticidade sináptica
  - Memória e Aprendizado
  - Desenvolvimento neuronal
- Receptores ionotrópicos e metabotrópicos
- Transportadores de Glutamato

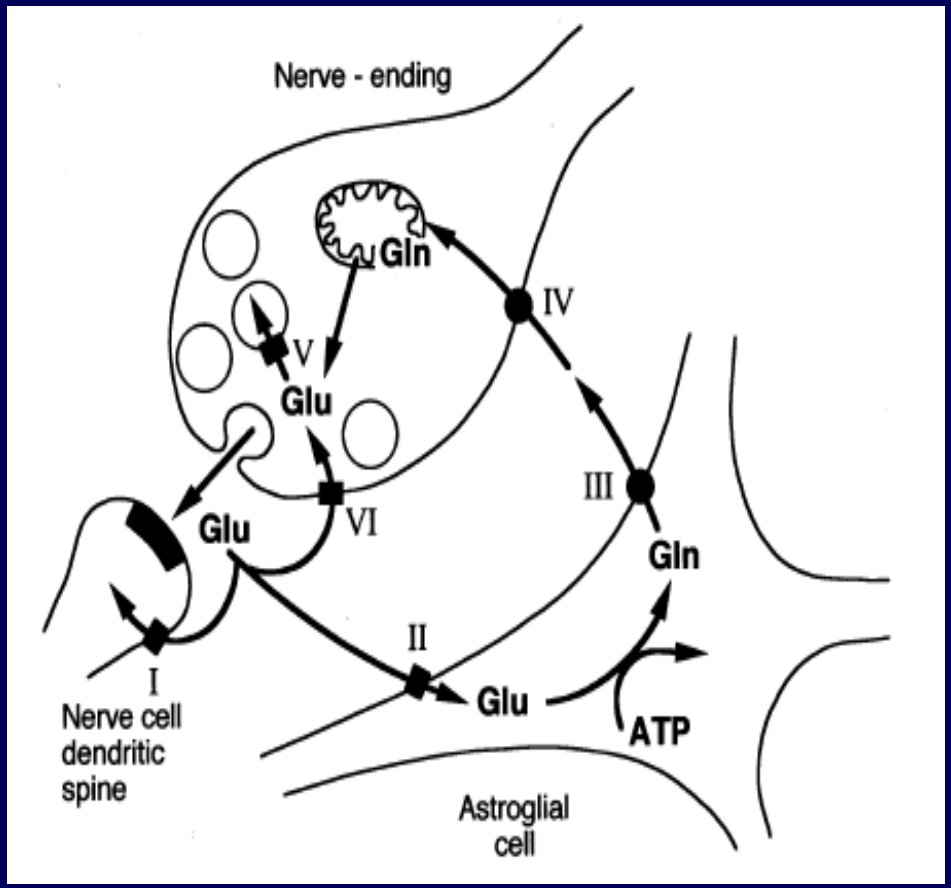
Liaw et al, Pain 2005; 115:60-70.

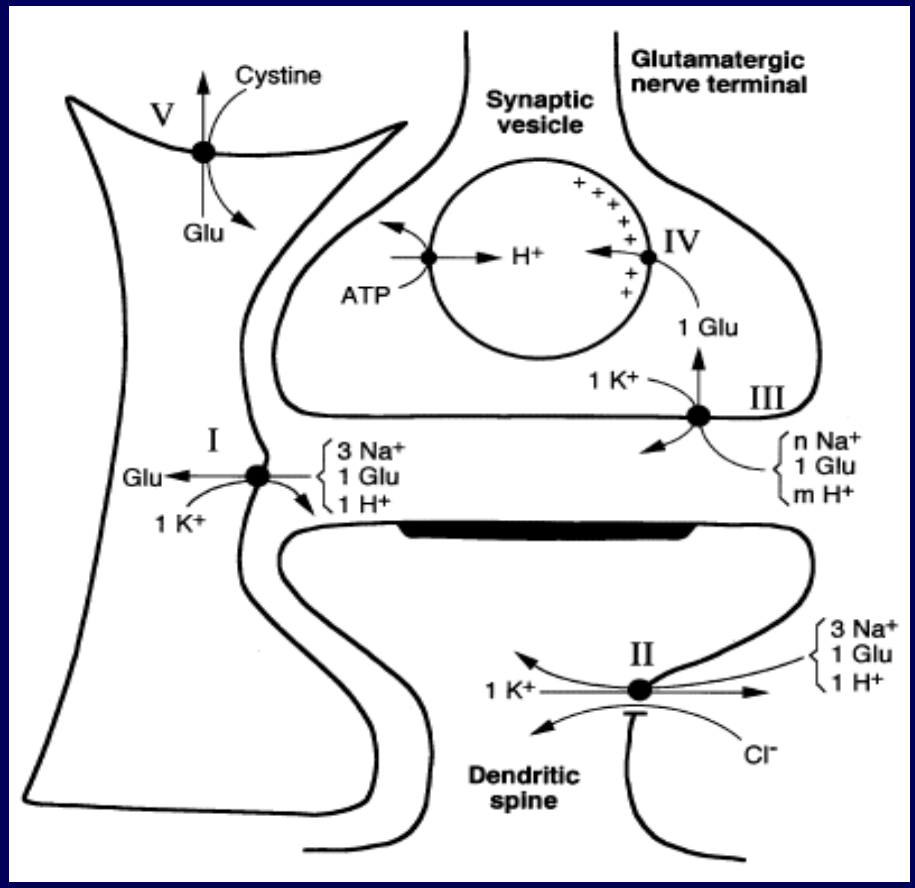
Receptores Glutamatérgicos e Dor

- NMDA
  - 7 subunidades (N1 e N2B)
  - Sítios modulatórios
  - Bloqueio por íon Magnésio
  - Ativação voltagem dependente
  - Papel dor persistente/patológica

Bleakman et al. Sem Cell Develop Biol 2006; 17:592-604.

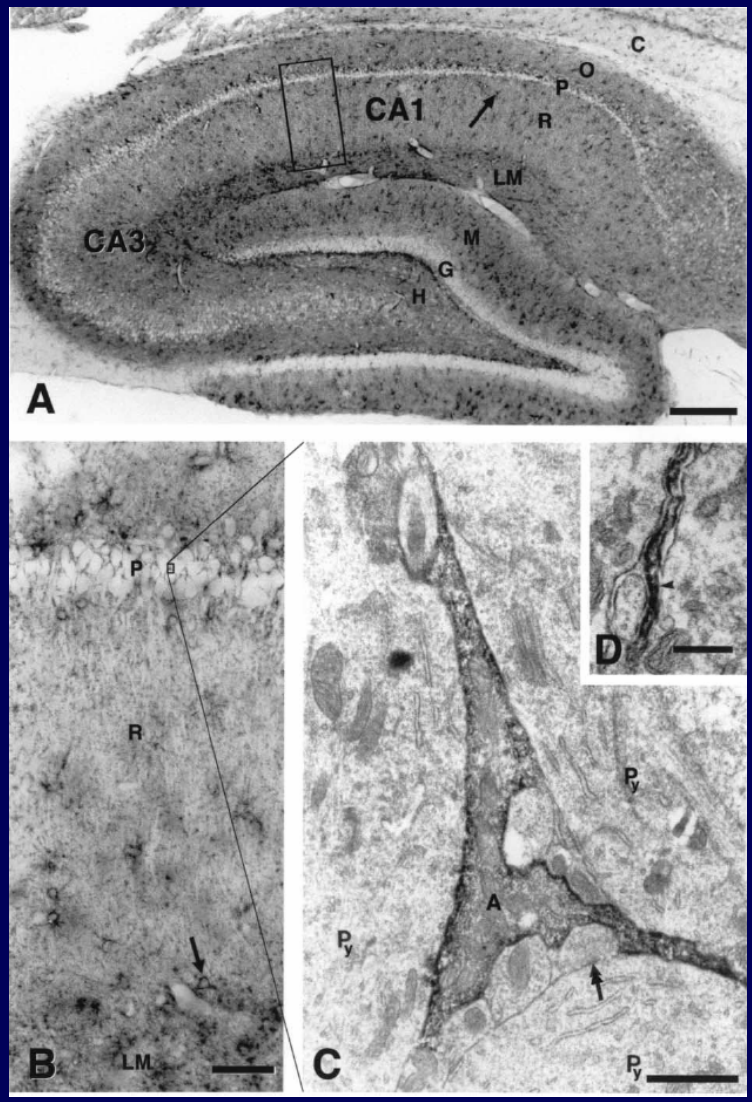
Transportadores de Glutamato e Dor

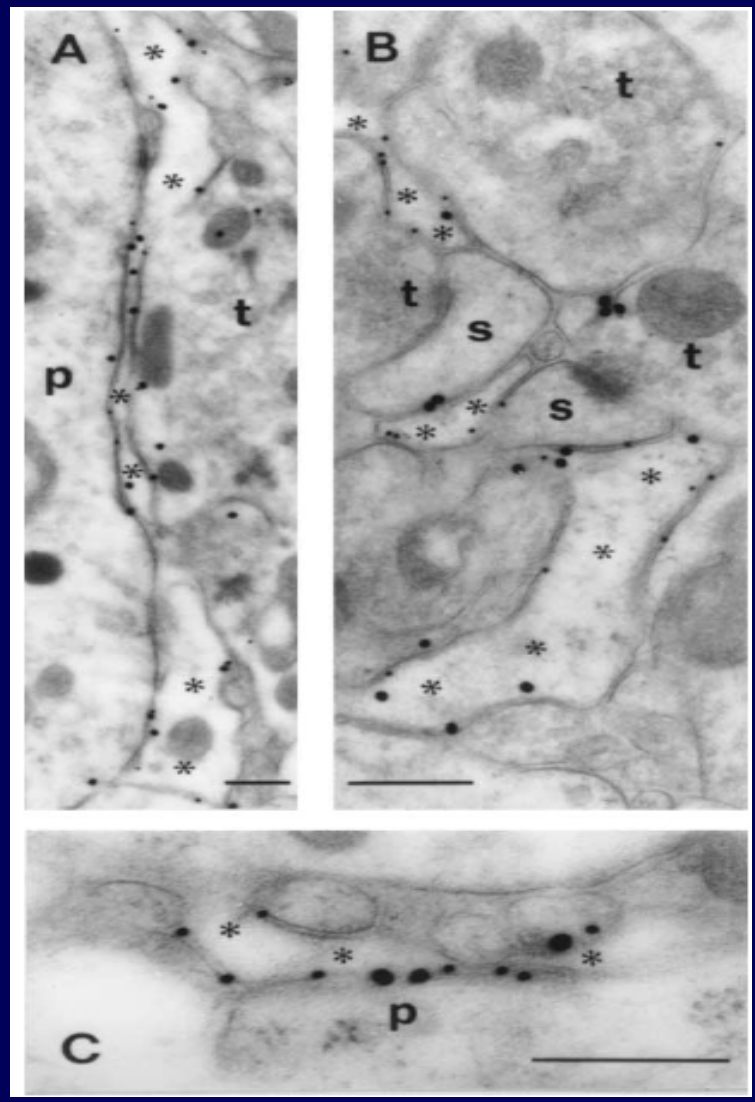




Liaw et al, Pain 2005; 115:60-70.

Transportadores de Glutamato e Dor





Danbolt C. Prog Neurobiol 2001; 1-105.

Hui Nie and Han-Rong Weng
J Neurophysiol 101:2041-2051, 2009. First published Feb 11, 2009; doi:10.1152/jn.91138.2008

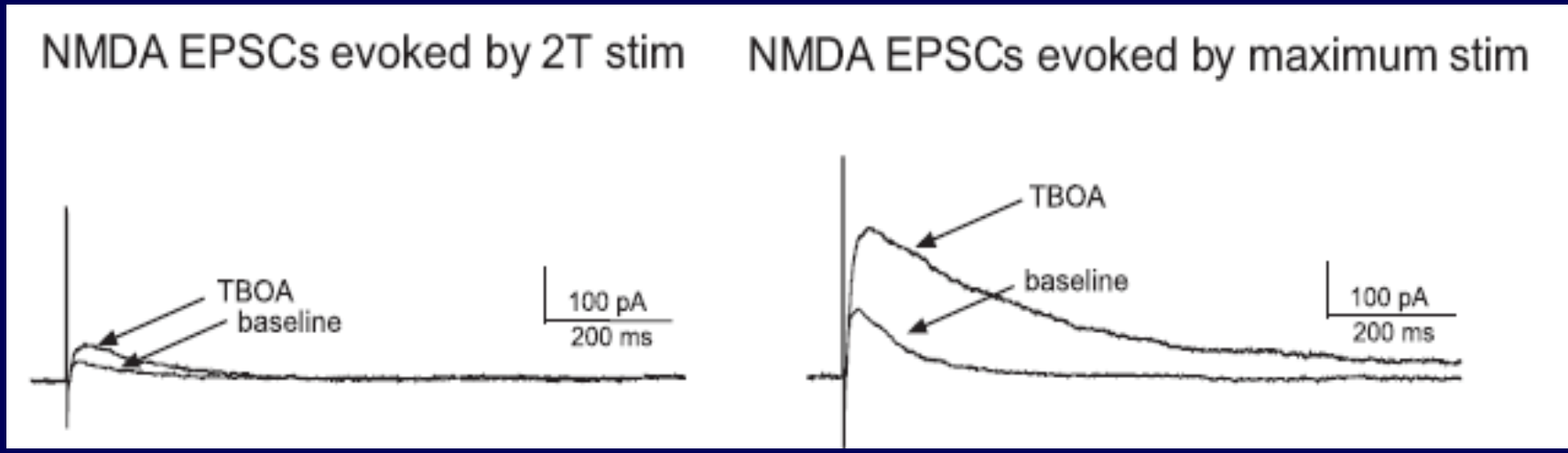
DISCUSSÃO DE ARTIGO

Glutamate Transporters Prevent Excessive Activation of NMDA Receptors and Extrasynaptic Glutamate Spillover in the Spinal Dorsal Horn

Hui Nie and Han-Rong Weng

J Neurophysiol 101: 2041–2051, 2009.
First published February 11, 2009; doi:10.1152/jn.91138.2008.

Department of Anesthesiology and Pain Medicine, Division of Anesthesiology and Critical Care, The University of Texas M. D. Anderson Cancer Center, Houston, Texas



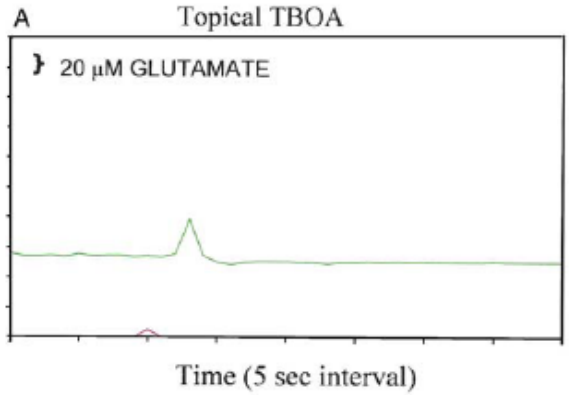
DISCUSSÃO DE ARTIGO

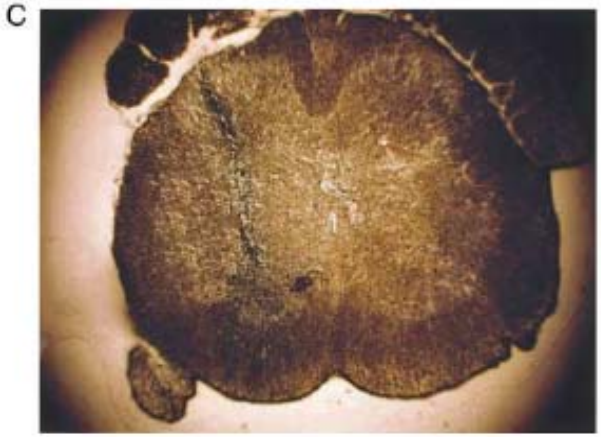
PAIN
www.elsevier.com/locate/pain

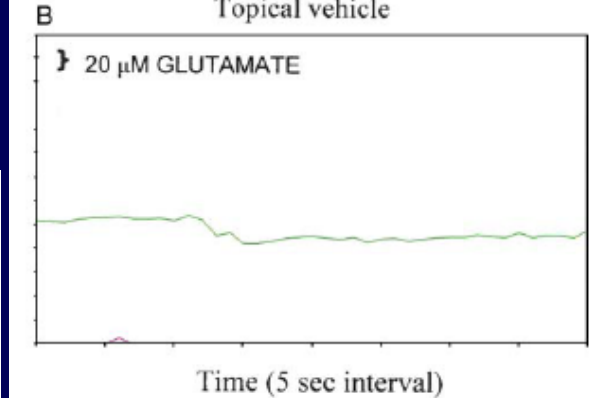
Spinal glutamate uptake is critical for maintaining normal sensory transmission in rat spinal cord

Wen-Jinn Liaw[a,b], Robert L. Stephens Jr[c], Brian C. Binns[c], Yachun Chu[a,d], Jehuda P. Sepkuty[e], Roger A. Johns[a], Jeffery D. Rothstein[e], Yuan-Xiang Tao[a,*]

Pain 115 (2005) 60–70



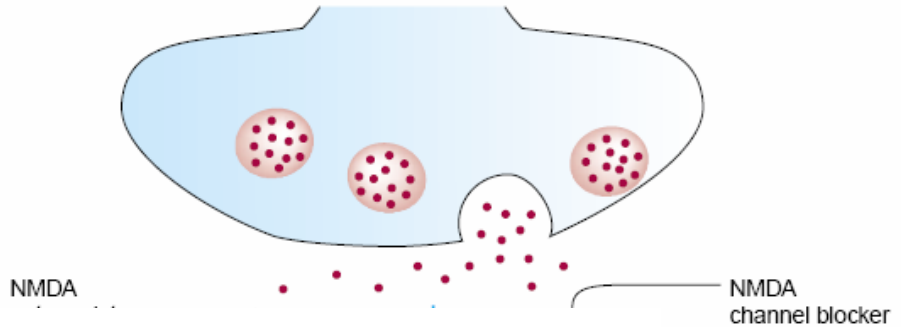


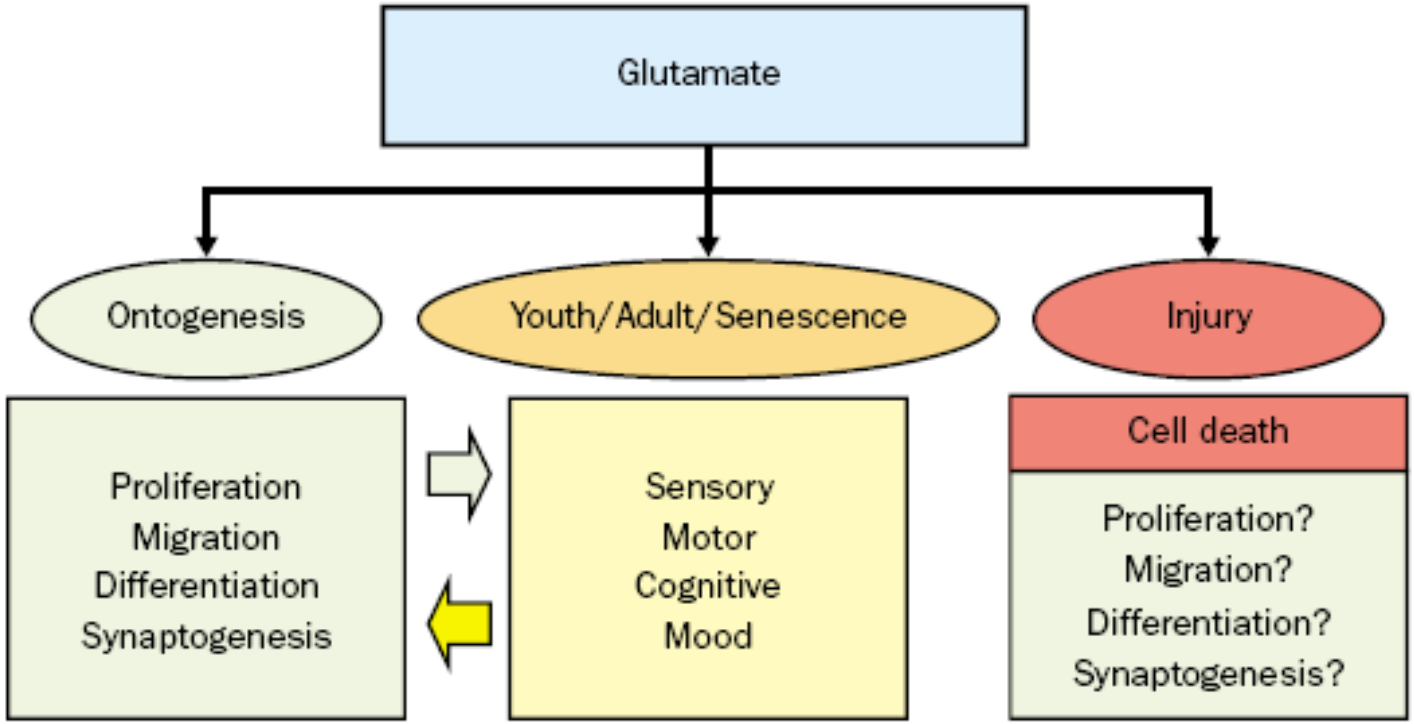


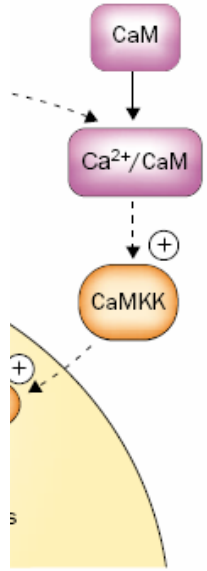
DISCUSSÃO DE ARTIGO

Why did NMDA recepto trials for stroke and tra

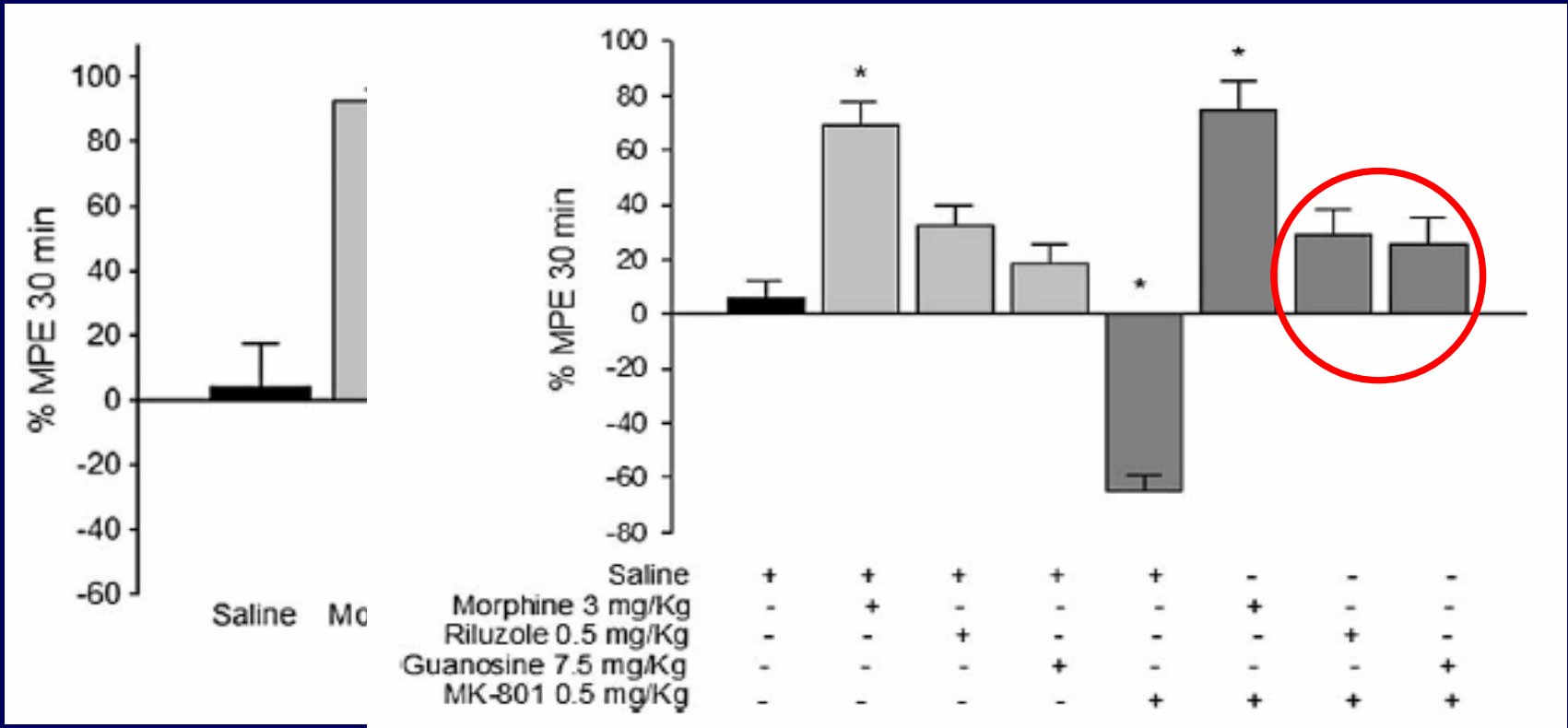
Chrysanthy Ikonomidou and Lechoslaw Turski





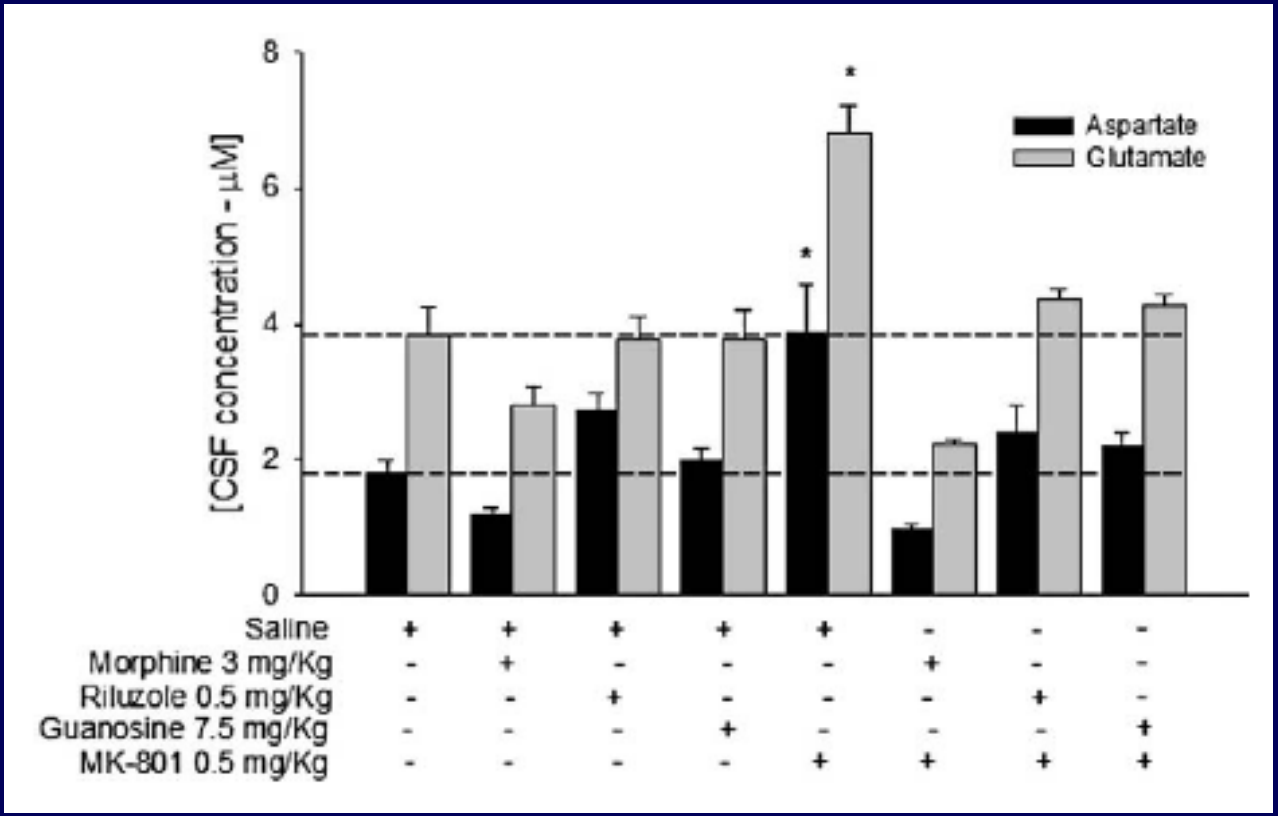


RESULTADOS



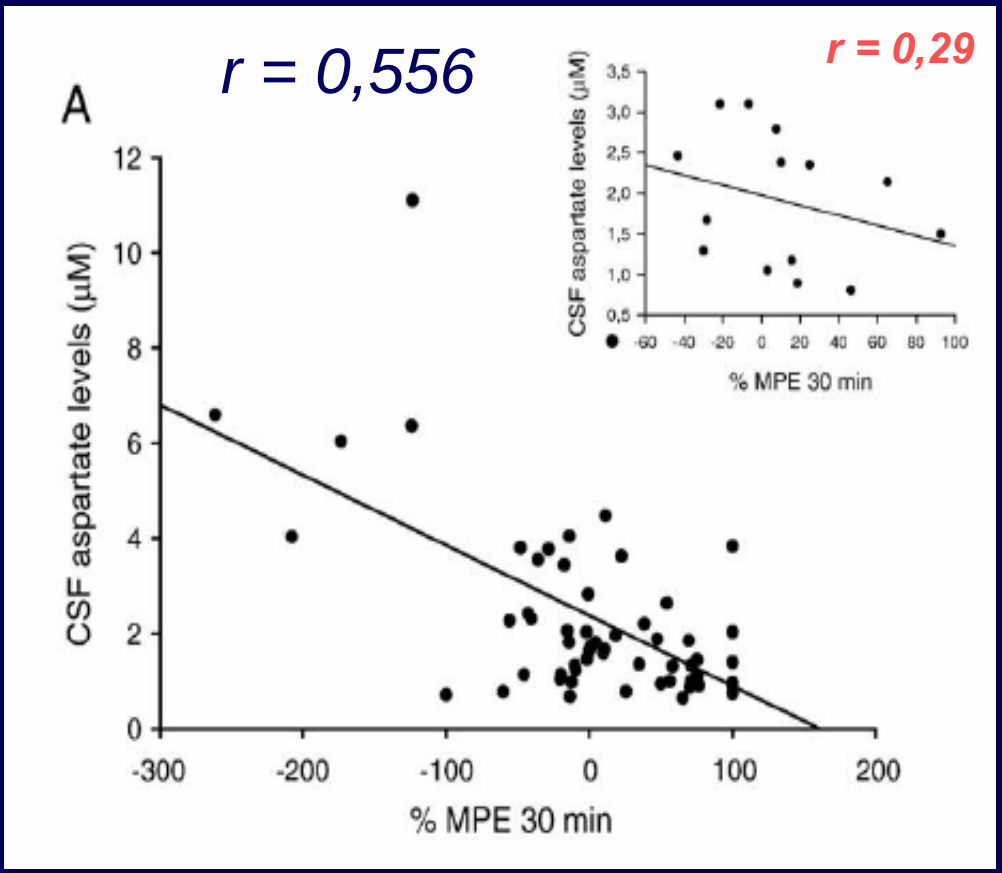
Schmidt et al., Pharmacol Biochem Behav 2008; no prelo.

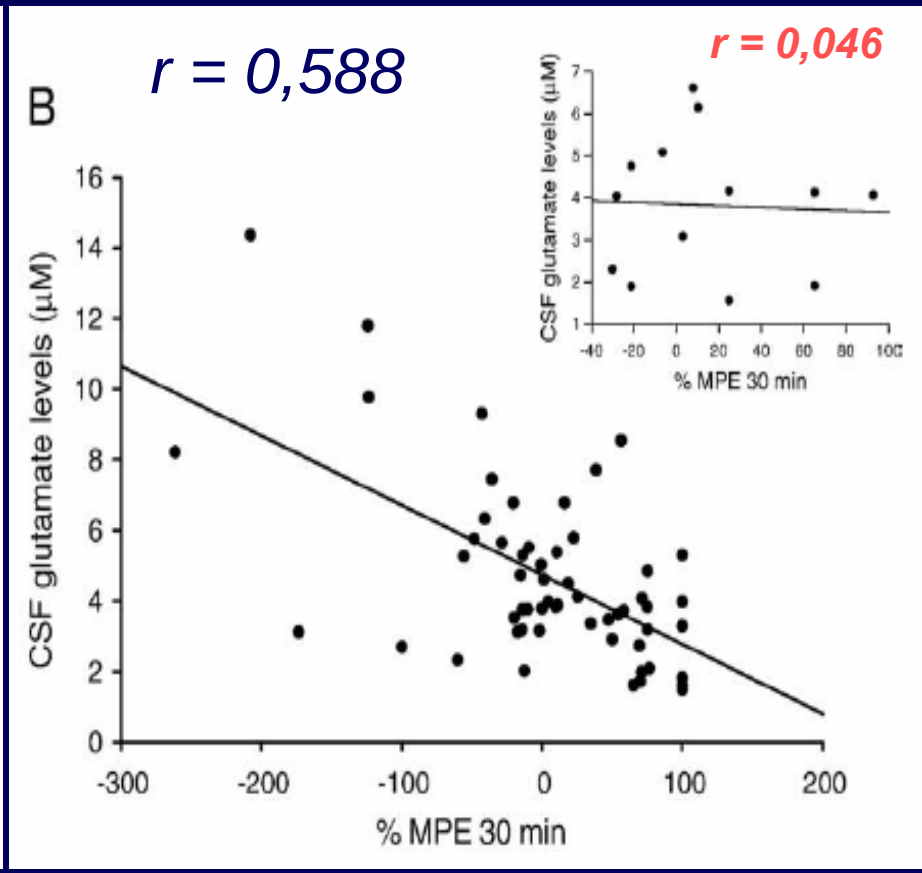
RESULTADOS



Schmidt et al., Pharmacol Biochem Behav 2008; no prelo.

RESULTADOS





Schmidt et al., Pharmacol Biochem Behav 2008; no prelo.

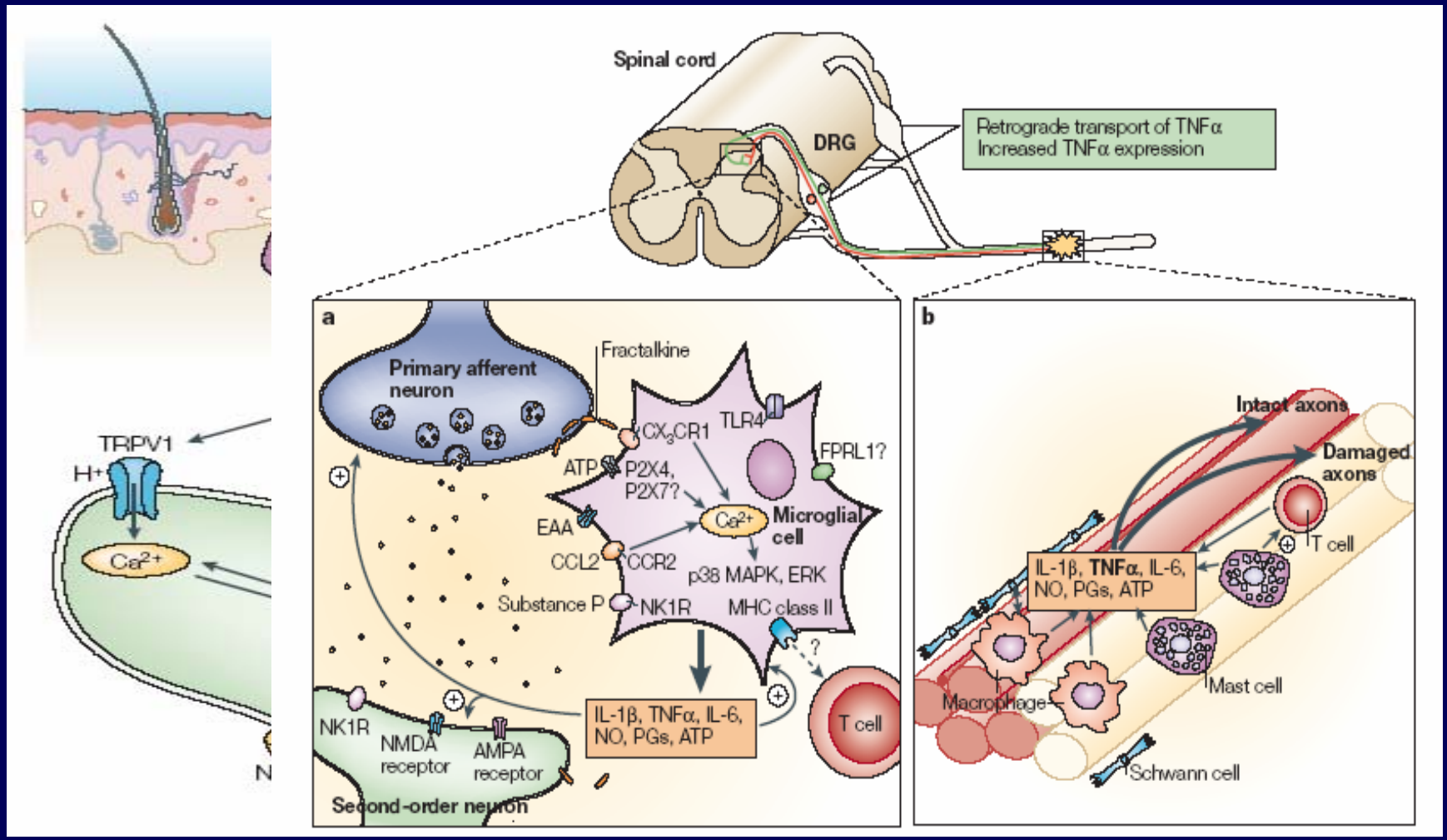
European Journal of Neuroscience, Vol. 22, pp. 1445–1454, 2005

Fyn kinase-mediated phosphorylation of NMDA receptor NR2B subunit at Tyr1472 is essential for maintenance of neuropathic pain

Tetsuya Abe,[1,2] Shinji Matsumura,[1] Tayo Katano,[1] Tamaki Mabuchi,[1] Kunio Takagi,[1] Li Xu,[1] Akitsugu Yamamoto,[3] Kotaro Hattori,[4] Takeshi Yagi,[4] Masahiko Watanabe,[5] Takanobu Nakazawa,[6] Tadashi Yamamoto,[6] Masayoshi Mishina,[7] Yoshihide Nakai[2] and Seiji Ito[1]

Departments of [1]Medical Chemistry and [2]Psychosomatic Medicine, Kansai Medical University, Moriguchi 570-8506, Japan
[3]Nagahama Institute of Bio-Science and Technology, Nagahama 526-0829, Japan
[4]KOKORO Biology Group and CREST, Laboratories for Integrated Biology, Graduate School of Frontier Biosciences, Osaka University, Suita 565-0871, Japan
[5]Department of Anatomy, Hokkaido University School of Medicine, Sapporo 060-8638, Japan
[6]Division of Oncology, Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan
[7]Department of Molecular Neurobiology and Pharmacology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan

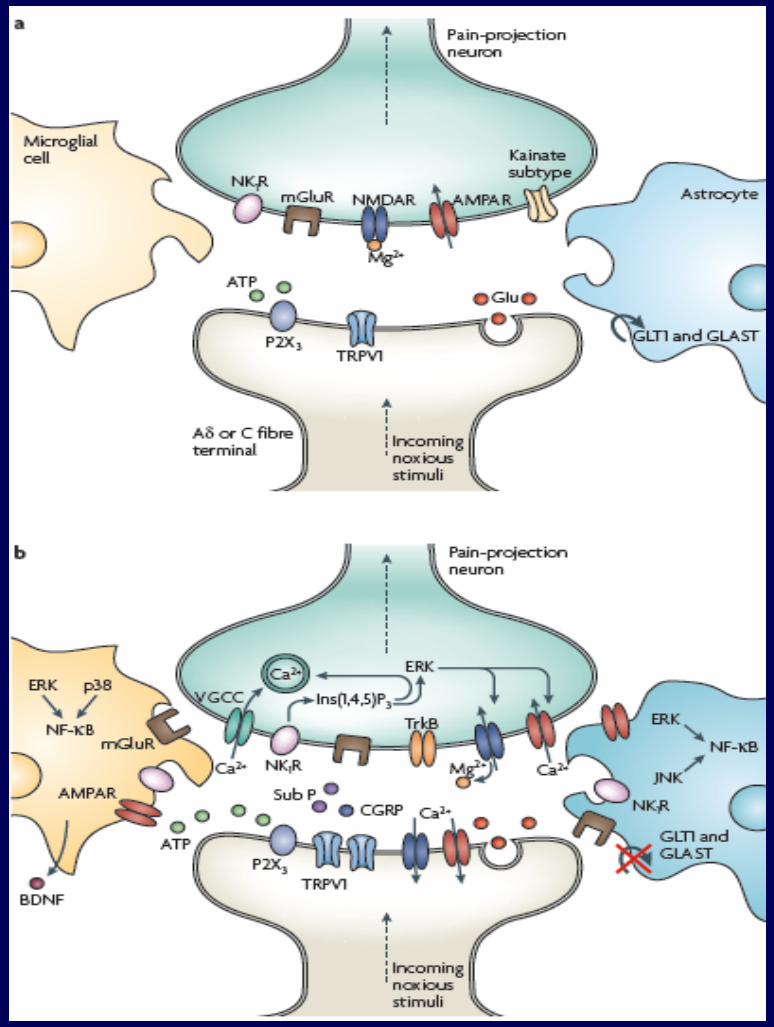
Sistema Imune e Dor

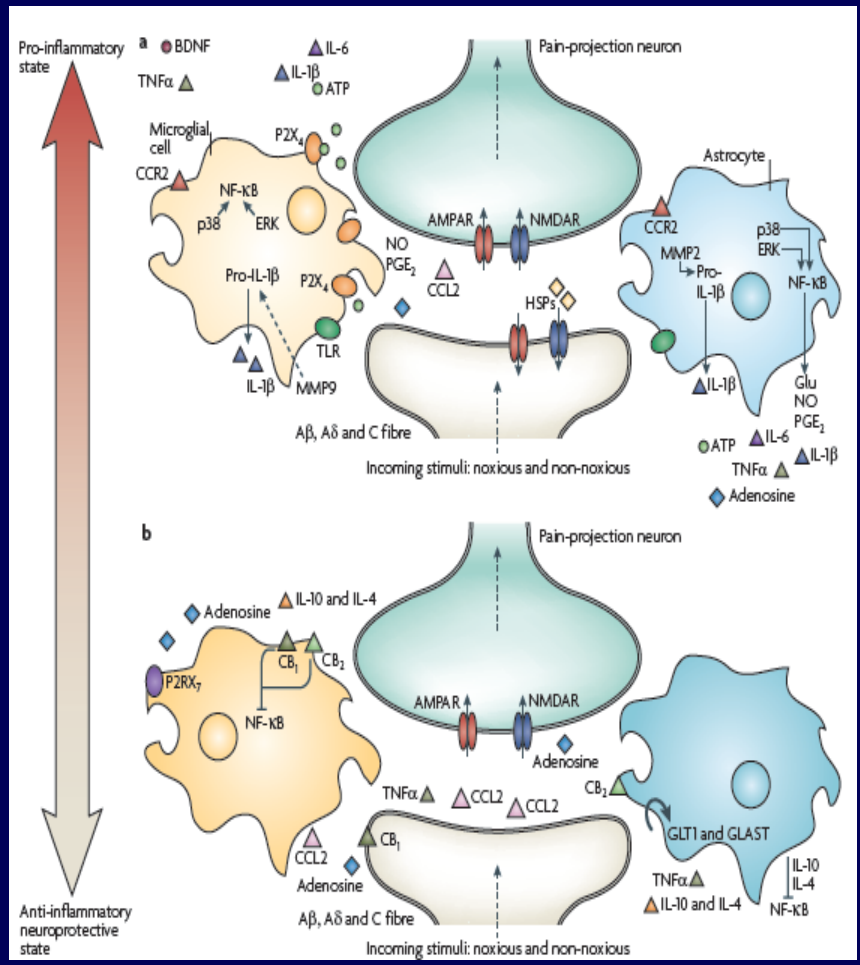


Marchand F. Nature Neurosci 2005; 6:521-31

Mecanismos de Transmissão da dor

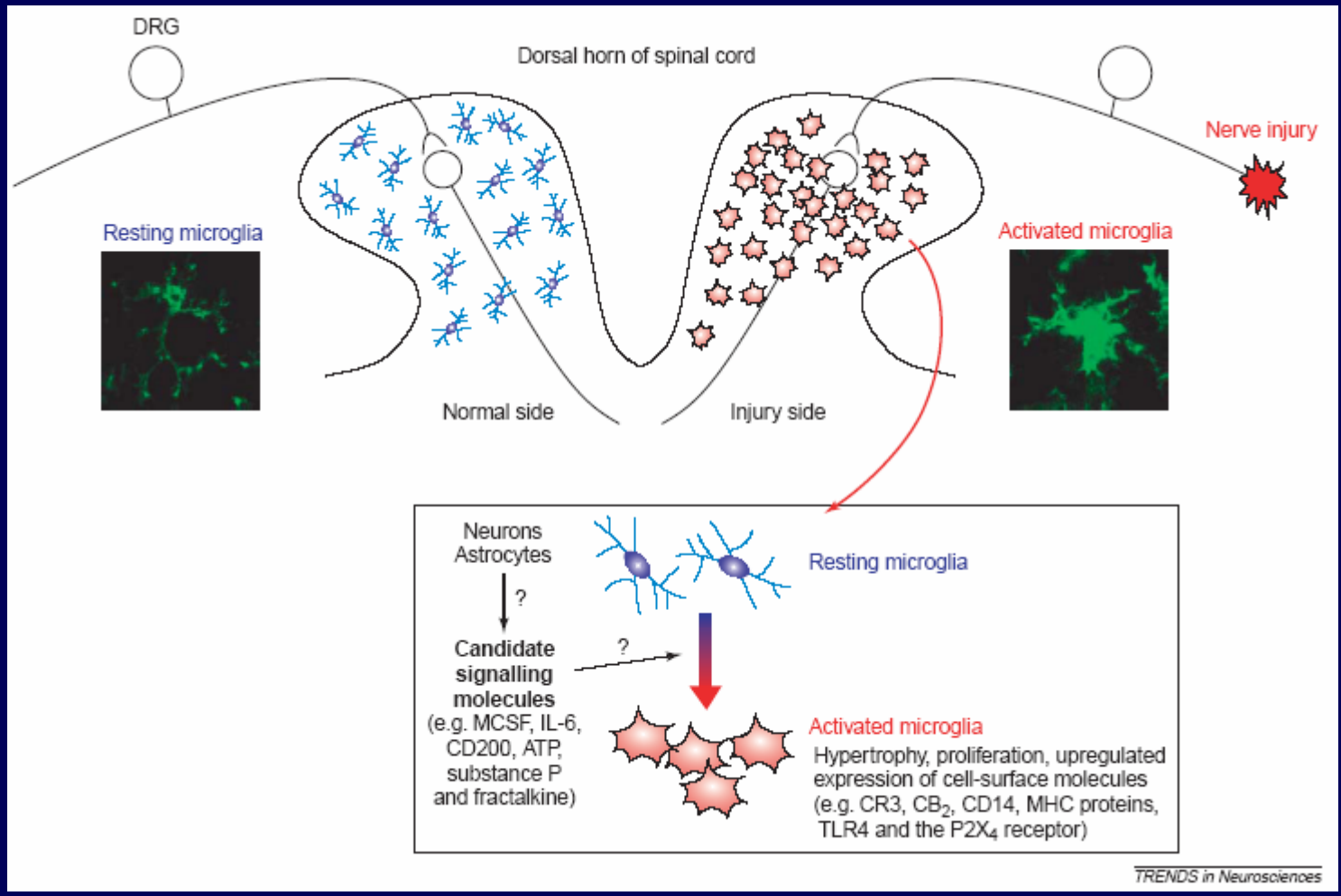
O papel da Glia





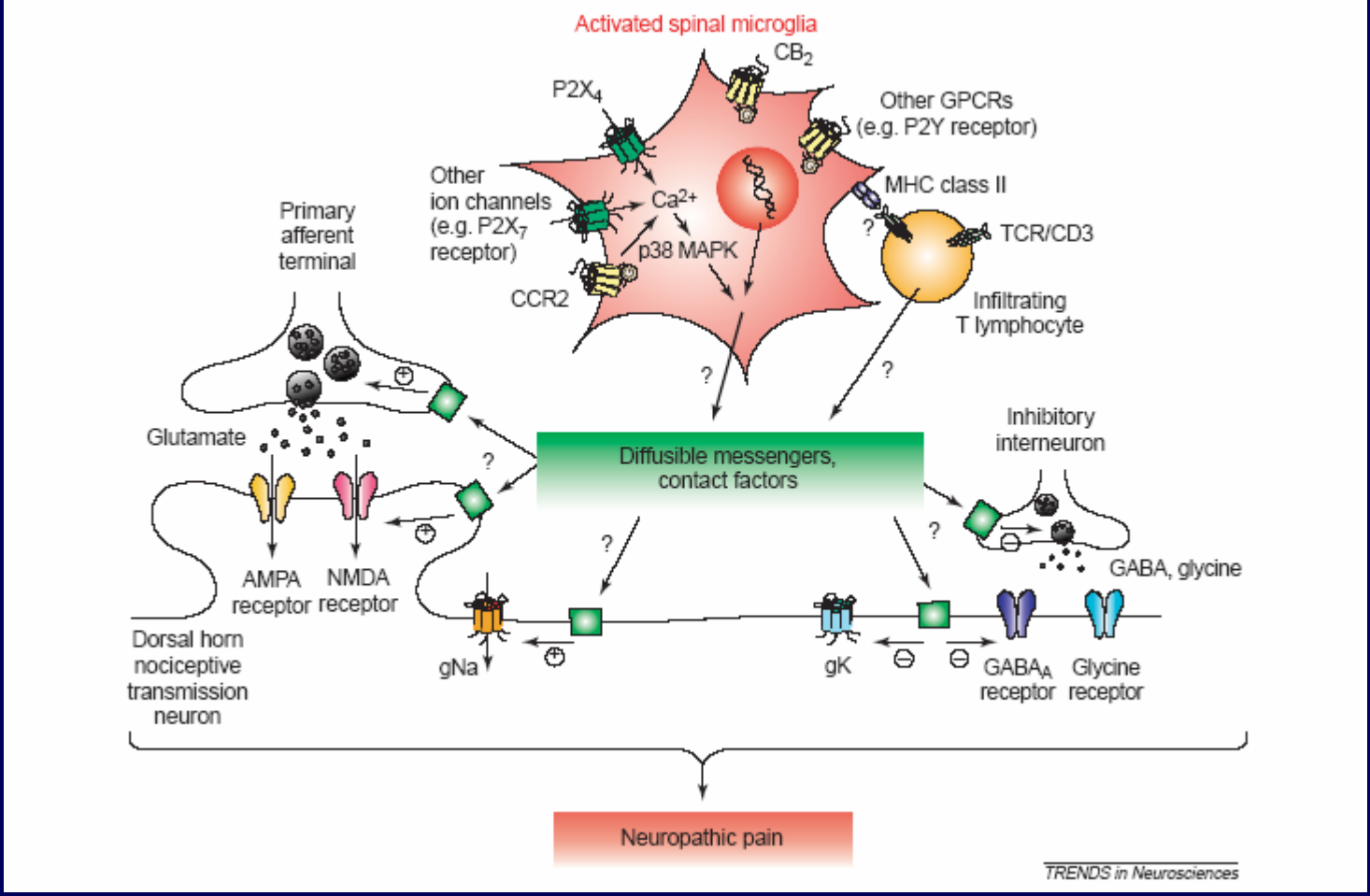
Milligan and Watkins, Nat Rev 2009; 10:23-36.

O papel da glia na dor



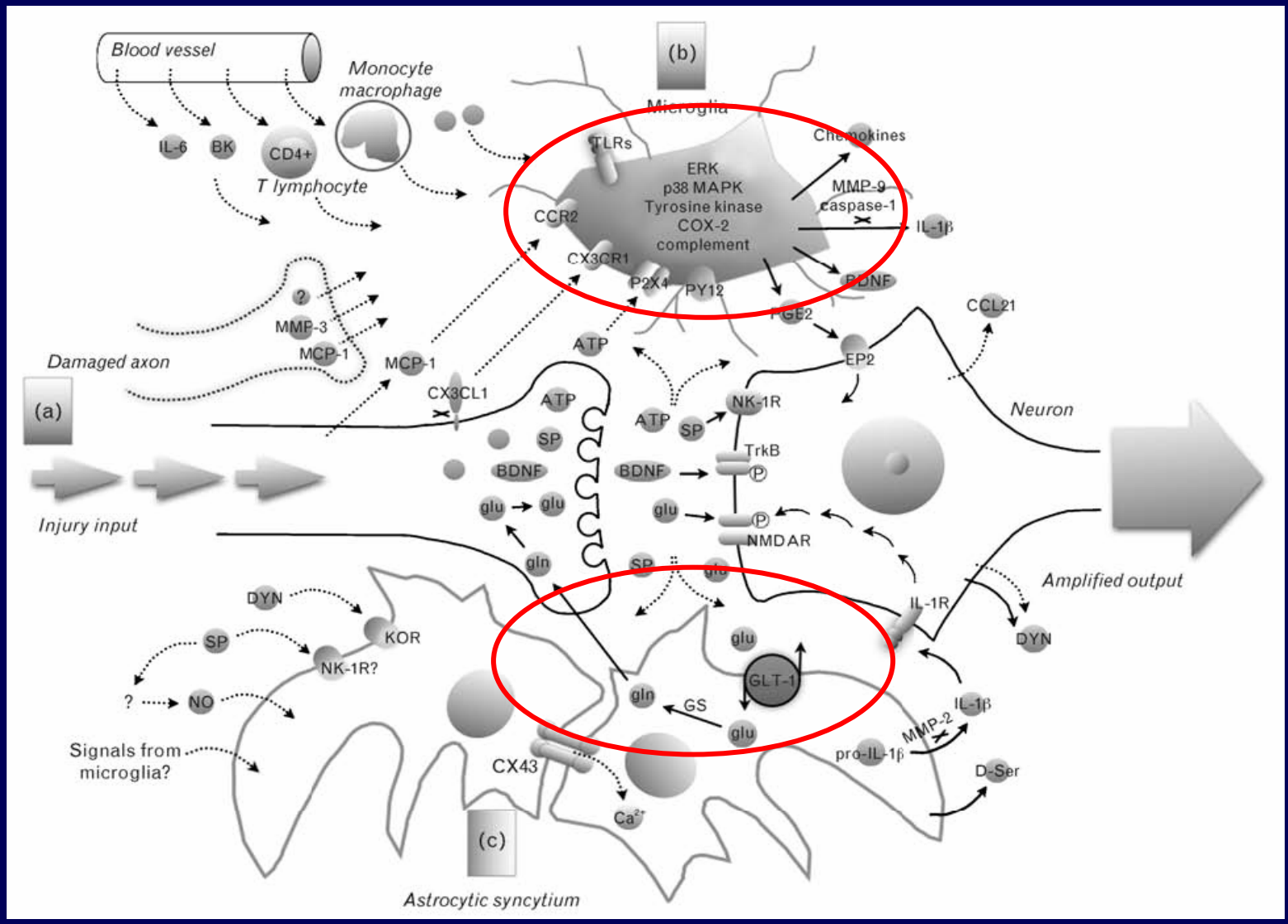
Tsuda et al., Trends Neurosci 2005; 28 :101-107

O papel da glia na dor



Tsuda et al., Trends Neurosci 2005; 28 :101-107

O papel da glia na dor



Ren and Dubner. Curr Opin Anesthesiol 2008; 21:570-9.

DISCUSSÃO DE ARTIGO

NEURON–GLIA INTERACTIONS

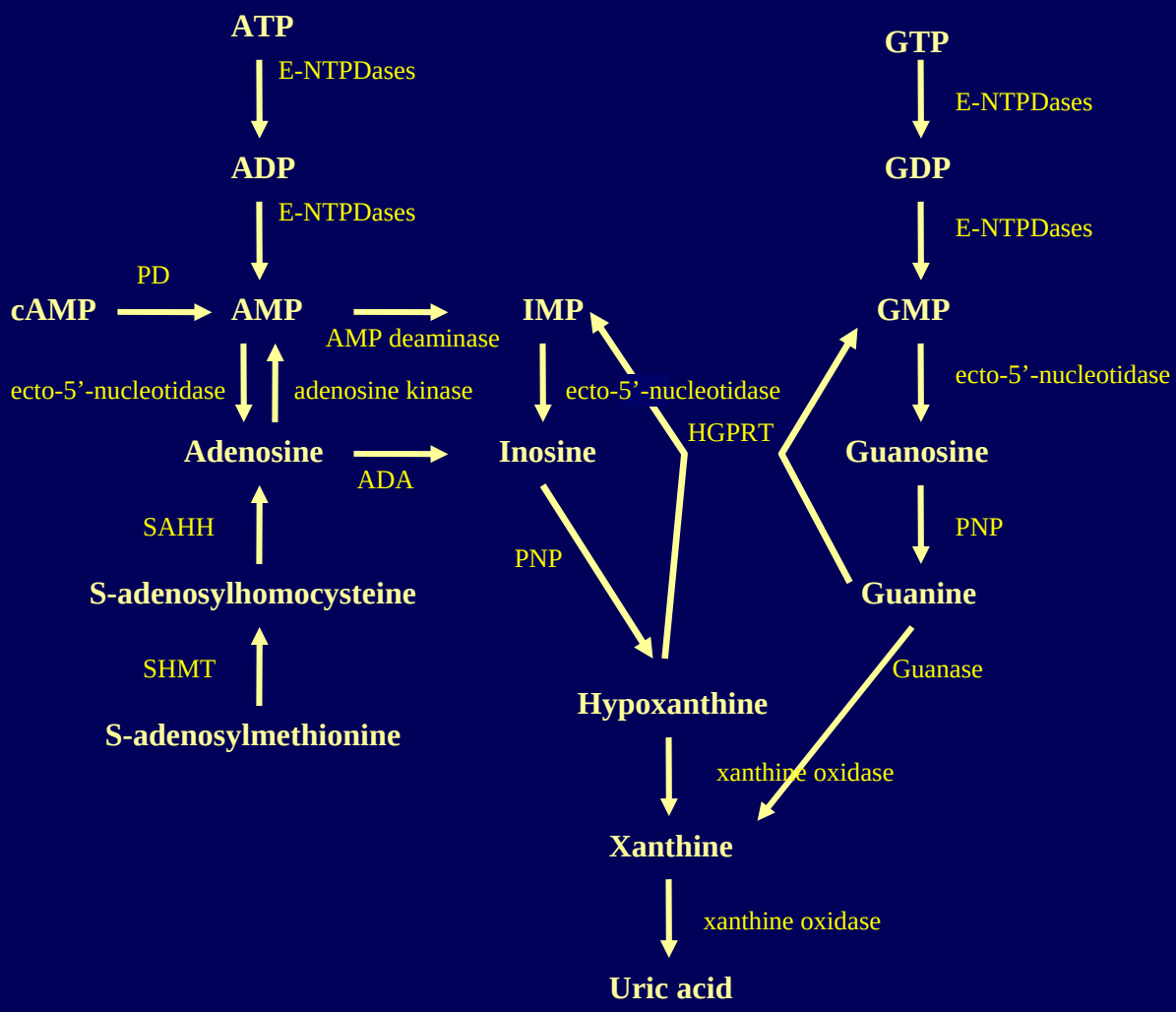
Pathological and protective roles of glia in chronic pain

Erin D. Milligan and Linda R. Watkins‡*

NATURE REVIEWS | NEUROSCIENCE VOLUME 10 | JANUARY 2009

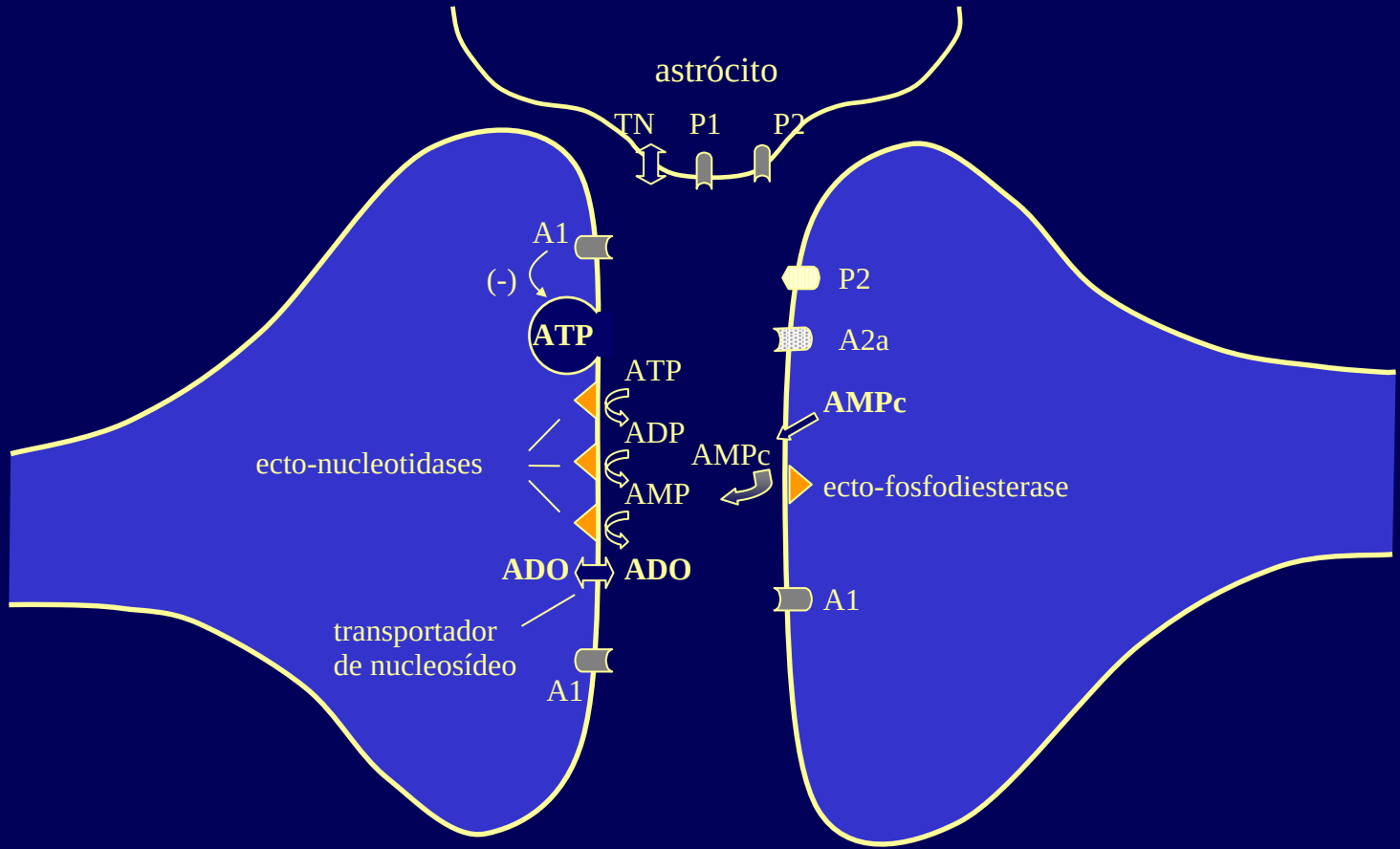
Ativação Glial na Dor Crônica – Toxicidade ou Neuroproteção ?

Sistema Purinérgico



Schmidt et al., Pharmacol Therap 2007; 116(3):401-416.

Sistema Purinérgico



Schmidt et al., Pharmacol Therap 2007; 116(3):401-416.

Efeitos da adenosina e seus análogos

- Efeitos tróficos
- Neuroproteção
- Anticonvulsivante endógeno
- Indutor do sono
- Inibição de liberação de neurotransmissores
- Inibição de atividade locomotora e coordenação motora
- Sedação
- Hipotermia
- Depressão cardiovascular e respiratória
- **Efeito antinociceptivo**
  - ATP – ação paradoxal – excitação neuronal

Receptores de adenosina A1

- Receptores A1- ↓ AMPc e Adenilato ciclase, ↑ IP_3, ↑ K^+, ↓ Ca^{2+}
- Amplamente distribuídos, alta expressão em hipocampo, córtex, cerebelo, **tálamo e substância cinzenta periaquedutal**
- Alta expressão de receptores A1 na **substância gelatinosa**
- ↓ liberação de neurotransmissores, como glutamato e dopamina; hiperpolarização neuronal
- Anticonvulsivante, neuroprotetor, anxiolítico, sedativo, depressor de locomoção e **ANALGESIA**

Mecanismos da ação antinociceptiva da adenosina

- Ação predominantemente central (espinhal e supra-espinhal)
- Ligação à proteína G, adenilato ciclase
- Hiperpolarização de neurônios no corno dorsal da medula – Inibição pós-sináptica da ativação de vias sensorias via susbtância P e NMDA
- Localização principal nos terminais sensoriais pós-sinápticos
- Inibição da liberação de aminoácidos excitatórios e substância P na medula espinhal

Papel das purinas na antinocicepção de outros agentes

- Morfina – liberação de adenosina; reversão parcial com xantinas
- Cafeína – ação pré-sináptica em terminais nervosos colinérgicos supra-espinhais
- Aminas biogênicas – serotonina e noradrenalina
- Tricíclicos – inibição da captação de adenosina; reversão parcial com xantinas
- Estimulação elétrica transcutânea – liberação de ATP

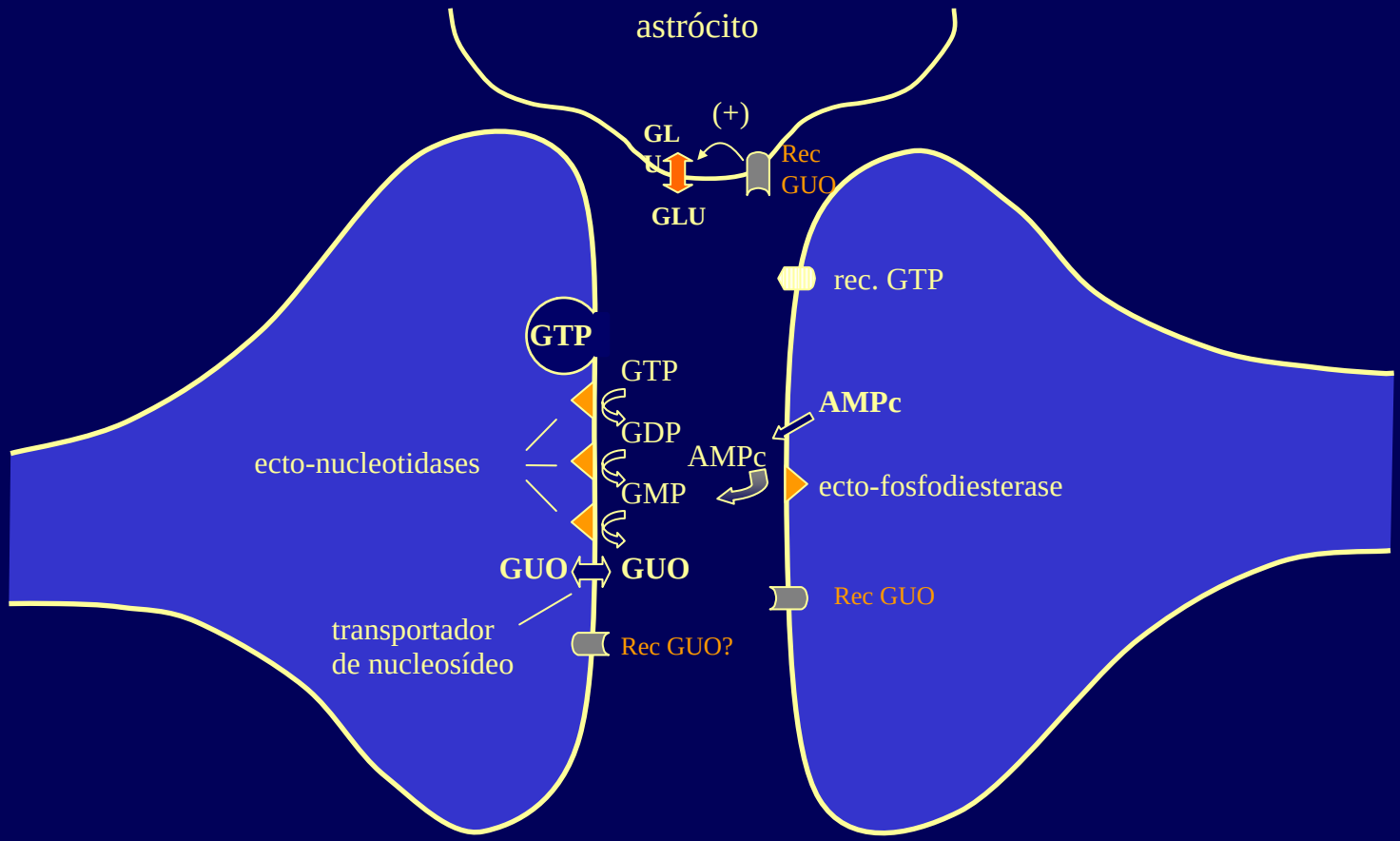
Available online at www.sciencedirect.com
ScienceDirect
Pharmacology & Therapeutics 116 (2007) 401–416
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Proposal of a guanine-based purinergic system in the mammalian central nervous system

André P. Schmidt [a], Diogo R. Lara [b], Diogo O. Souza [a,*]

[a] *Departamento de Bioquímica, ICBS, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[b] *Faculdade de Biociências, Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil*

Sistema Purinérgico da Guanina



Schmidt et al., Pharmacol Therap 2007; 116(3):401-416.

Derivados da guanina

- Analgesia mediada por outros integrantes do sistema purinérgico:
  - Guanina
  - Guanosina

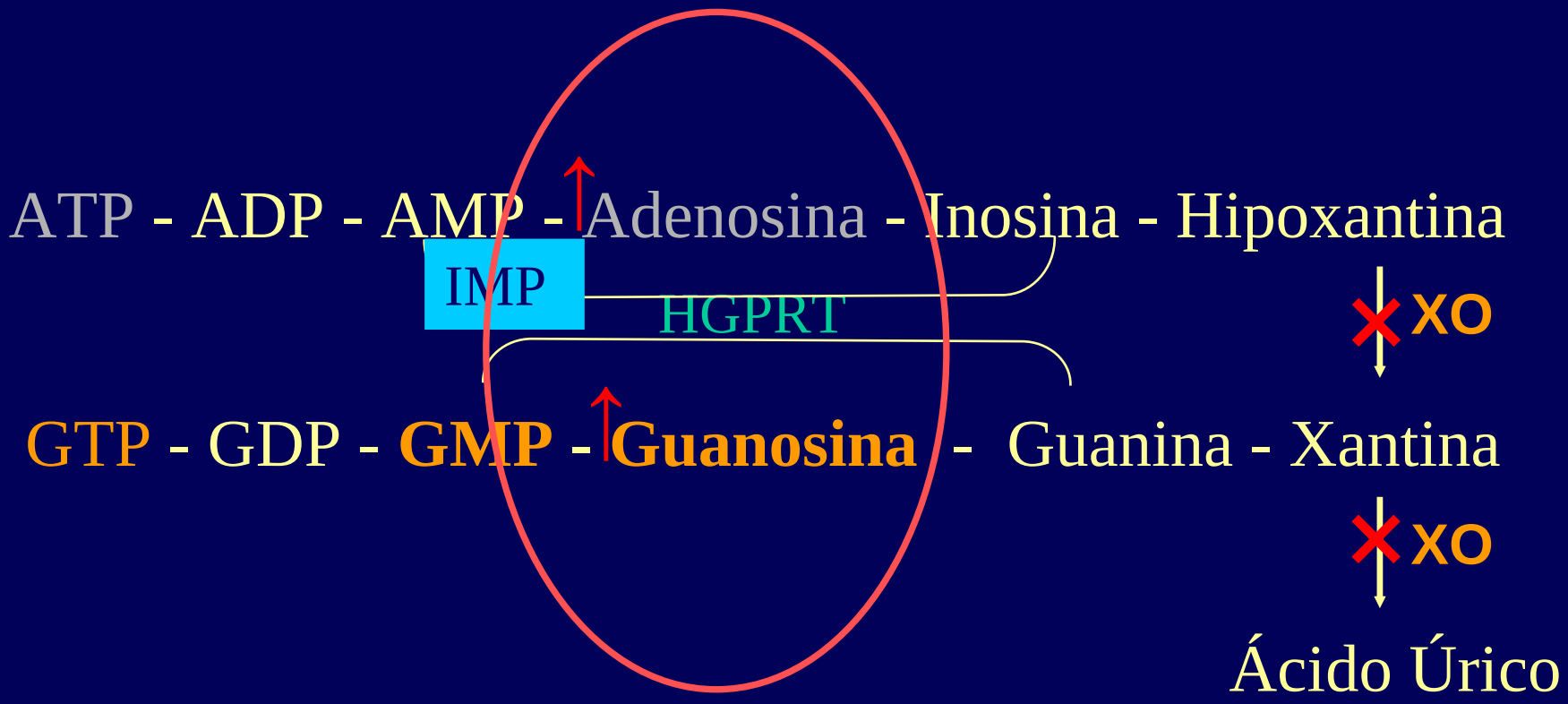
Schmidt et al., Brain Res 2000; 864: 40-3.

Schmidt et al., Eur J Pharmacol 2009; in press.

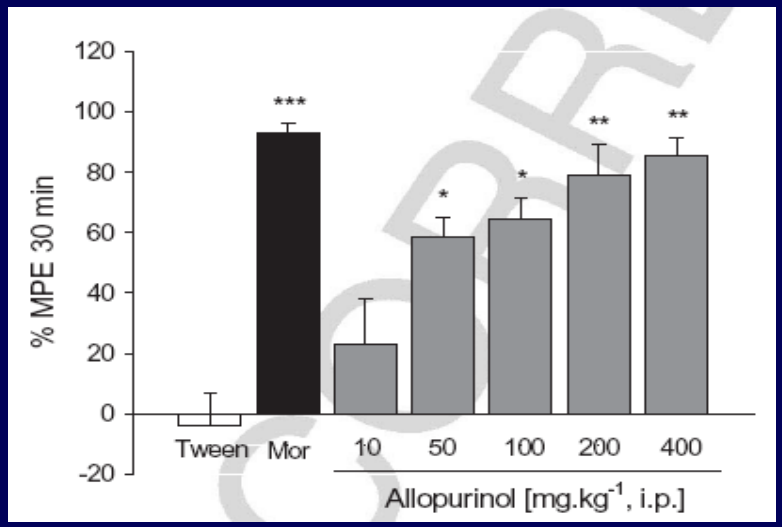
Schmidt et al., Brain Res 2008; 1234: 50-8..

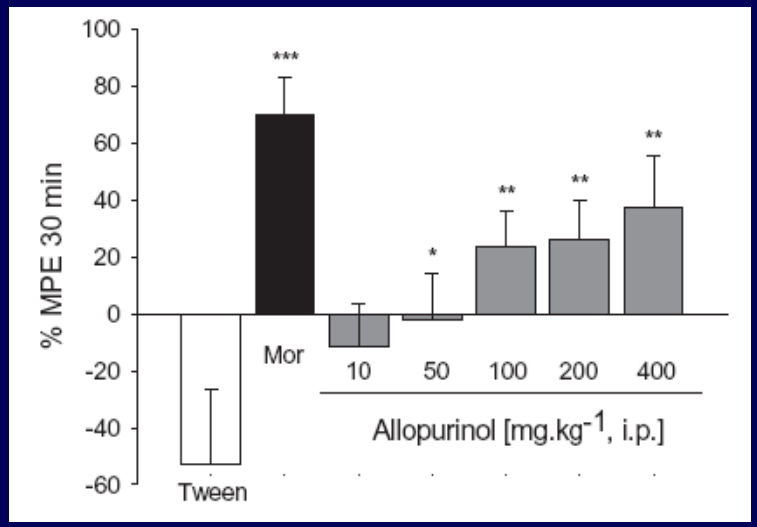
Schmidt at al., Neurochem Res 2005; 30(1): 69-73.

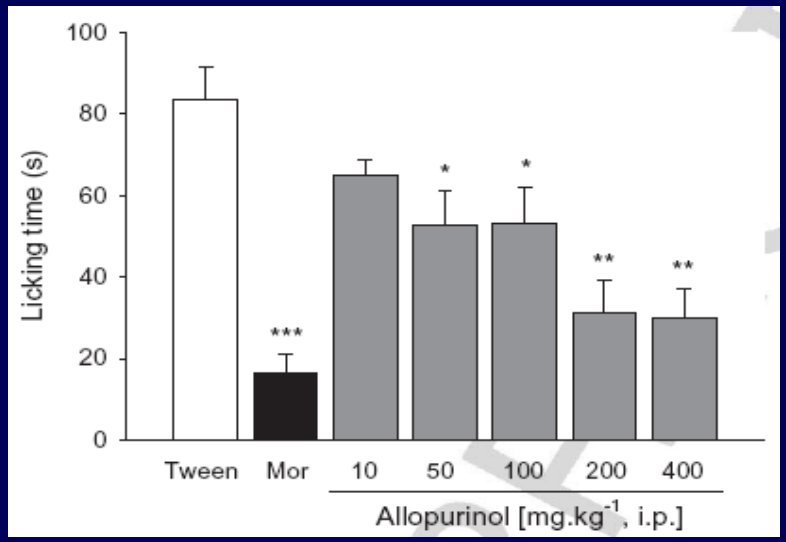
Alopurinol, um inibidor da xantina oxidase

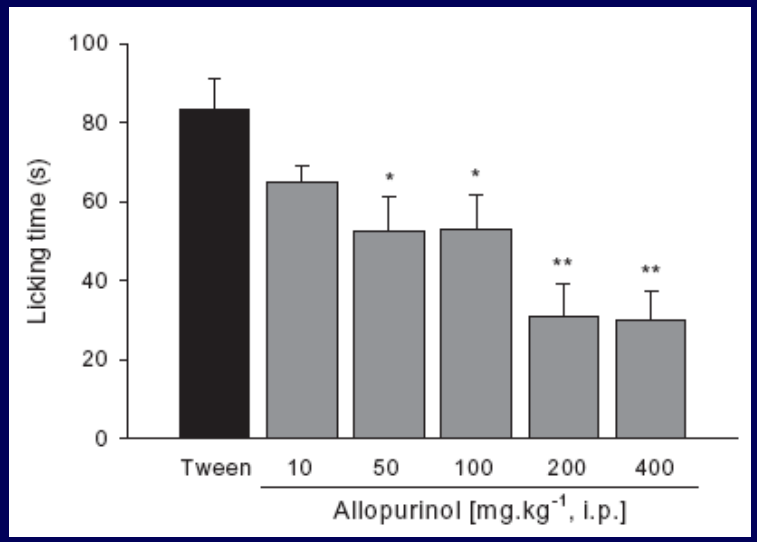


Alopurinol X Modelos de dor



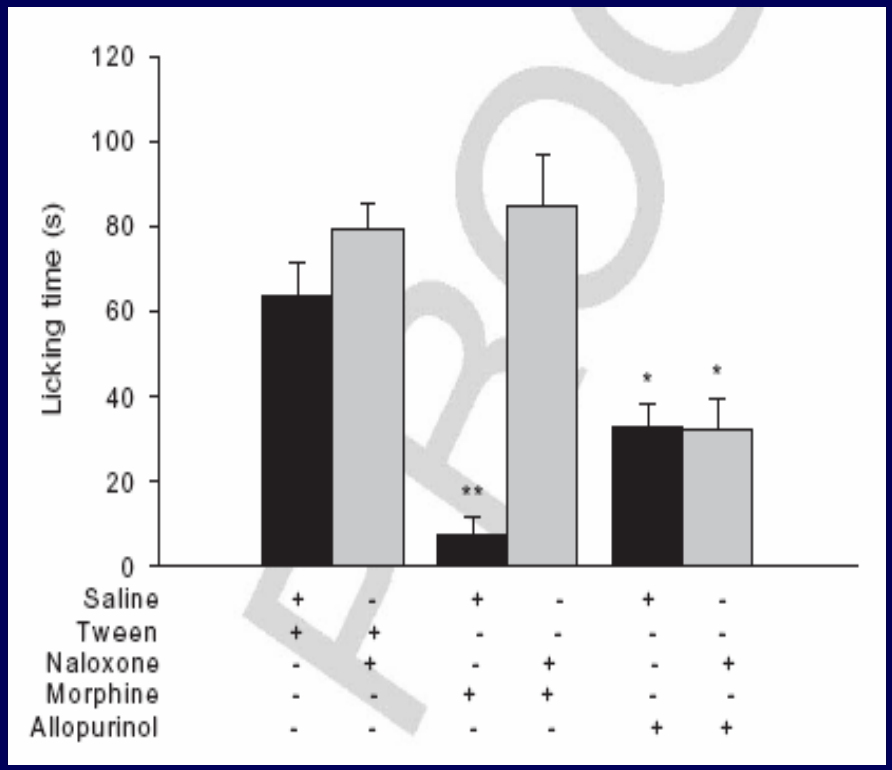


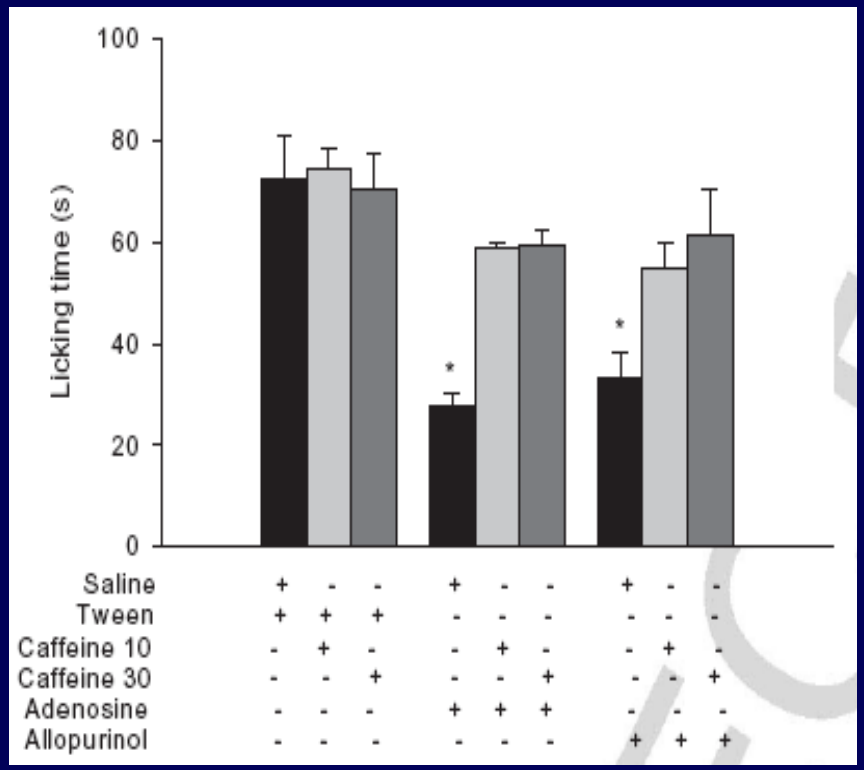




Schmidt et al., Br J Pharmacol 2009; no prelo.

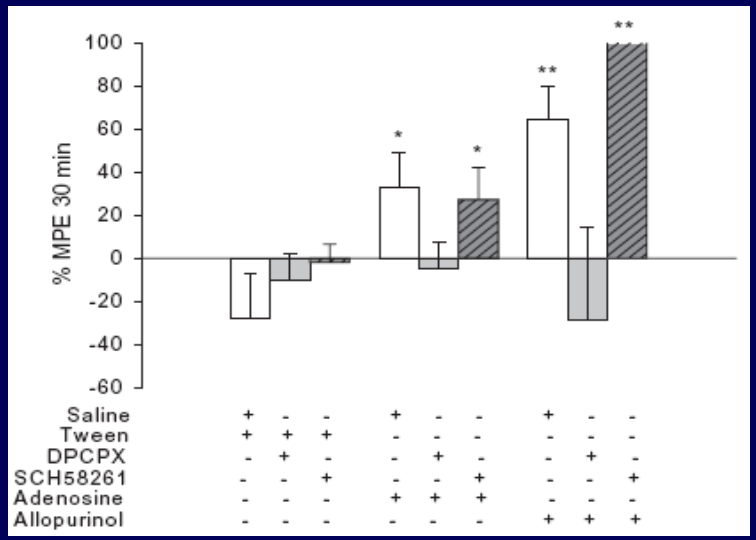
Alopurinol X Mecanismo de ação

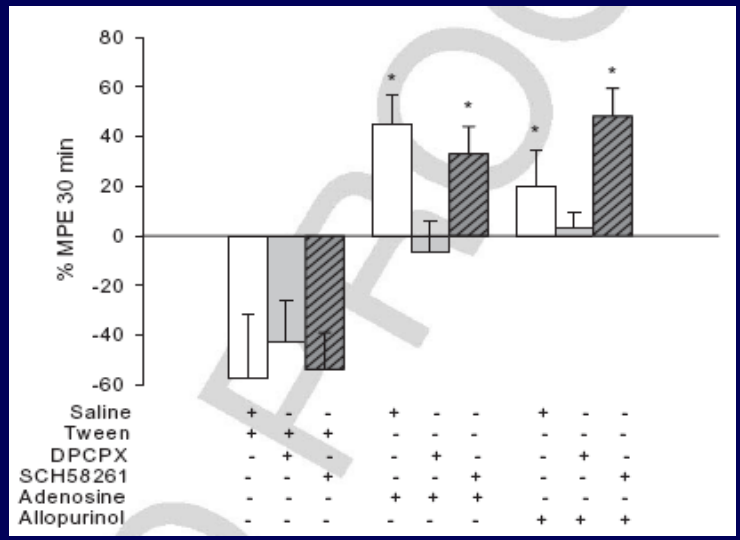


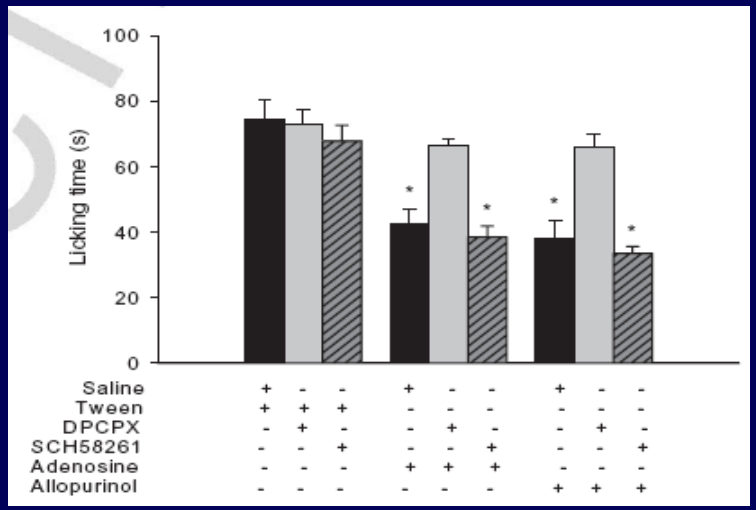


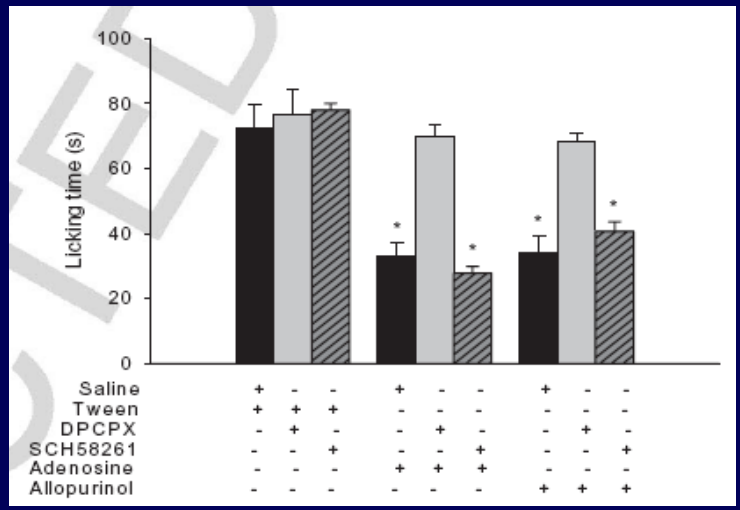
Schmidt et al., Br J Pharmacol 2009; no prelo.

Alopurinol X Mecanismo de ação









Schmidt et al., Br J Pharmacol 2009; no prelo.

Alopurinol X Comportamento

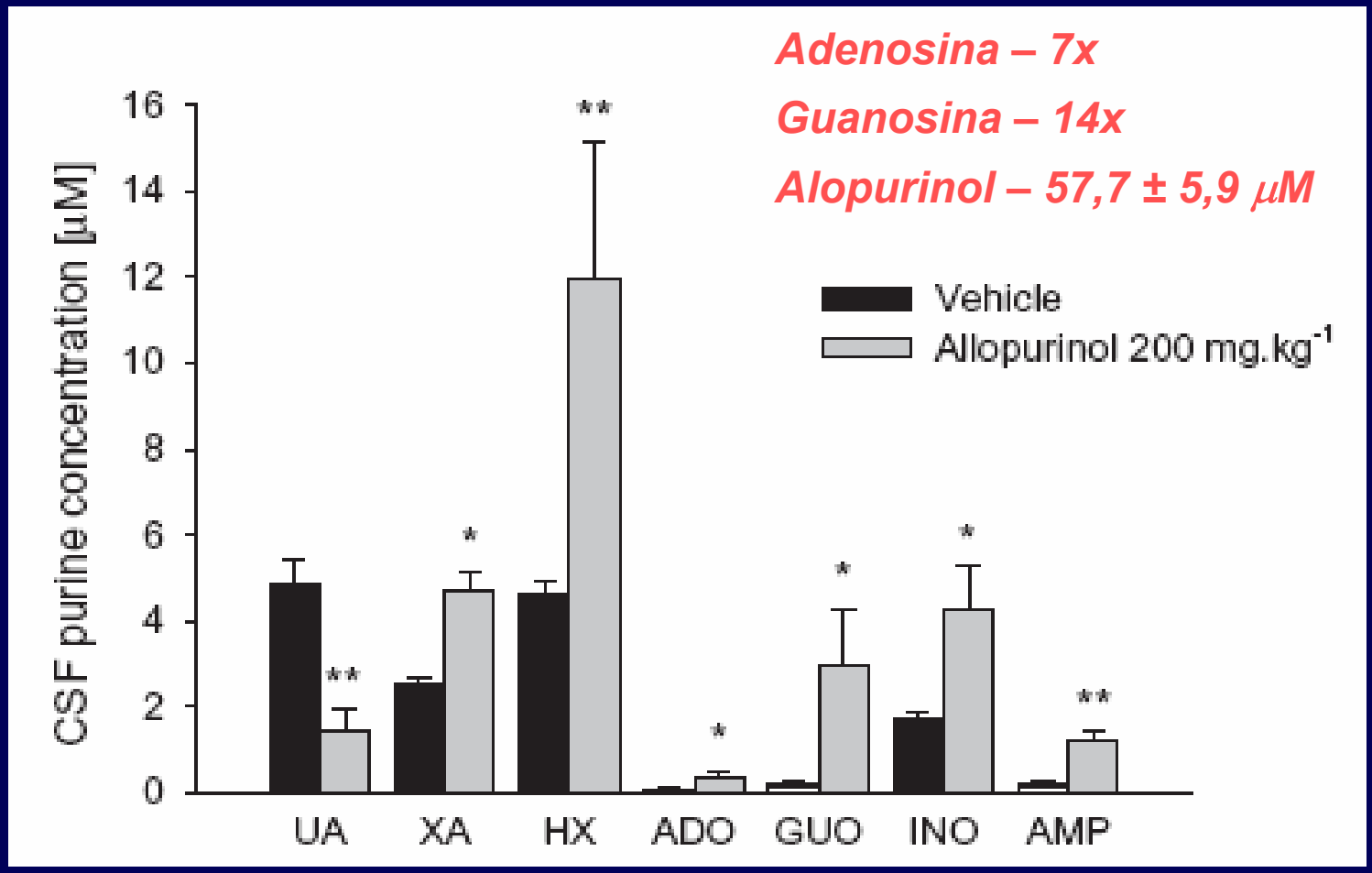
Table 1 Effects of allopurinol on the hole-board, rotarod and spontaneous locomotor activity tests, used in mice

Treatment	*Allopurinol (mg kg^{-1})*					
	Tween 10%	*10*	*50*	*100*	*200*	*400*
Latency to head-dip (s)	6.0 (0.9)	6.4 (0.8)	5.5 (0.9)	7.5 (0.2)	5.3 (0.7)	8.5 (0.7)
Head-dips (*n*)	50.1 (5.7)	56.0 (2.2)	49.7 (8.6)	43.5 (6.2)	47.0 (7.5)	35.0 (6.3)
Squares crossed (*n*)	42.1 (5.4)	40.7 (5.9)	44.0 (7.2)	47.7 (5.9)	46.0 (9.4)	21.7 (9.4)*
Rearings (*n*)	2.0 (0.8)	2.3 (0.8)	2.6 (0.9)	1.8 (1.0)	1.7 (0.8)	0.7 (0.3)*
Groomings (*n*)	1.6 (0.3)	1.5 (0.3)	0.8 (0.4)	1.2 (0.4)	1.6 (0.6)	1.3 (0.4)
Fecal boli (*n*)	0.8 (0.4)	1.2 (0.4)	1.2 (0.5)	1.0 (0.3)	1.5 (0.5)	0.8 (0.5)
Latency to fall (s)	56.4 (1.6)	50.6 (7.0)	58.0 (1.5)	50.8 (6.8)	56.2 (2.5)	34.5 (5.8)*
Crossings (*n*)	234 (28)	250 (37)	222 (10)	213 (15)	212 (19)	140 (14)*

Vehicle (10% Tween) or allopurinol was given i.p., 30 min prior to the behaviour measurements: latency to the first head-dip; head-dips; squares crossed; rearings; groomings; fecal boli; latency to fall (rotarod); number of crossings (spontaneous locomotor activity). $n = 8$ animals per group. *$P < 0.05$ compared with control (10% Tween), one-way ANOVA followed by Student–Newman–Keuls test.

Schmidt et al., Br J Pharmacol 2009; no prelo.

Alopurinol X Dosagem de purinas no LCR



Schmidt et al., Br J Pharmacol 2009; no prelo.

British Journal of Pharmacology (2009), 156, 4–6

0007-1188/08
www.brjpharmacol.org

COMMENTARY

Allopurinol for pain relief: more than just crystal clearance?

Mark Connor[1,2]

[1]*Pain Management Research Institute, Kolling Institute, University of Sydney at Royal North Hospital St Leonards, and* [2]*Brain and Mind Research Institute, University of Sydney, Camperdown, NSW, Australia*

Gout and pain are synonymous, and a study in this issue of the *BJP* reports a novel anti-nociceptive effect of allopurinol, the drug most commonly used to treat gout. Allopurinol works by inhibiting xanthine oxidase (XO), the enzyme responsible for converting hypoxanthine to uric acid which is deposited as crystals in the joints of gout sufferers. Hypoxanthine is a metabolite of, and a possible precursor to, adenosine. Schmidt *et al.*, find that acute inhibition of XO with allopurinol produces a modest adenosine A_1 receptor-mediated anti-nociceptive effect in common tests of chemical and thermal nociception in mice. A concomitant increase in cerebrospinal fluid levels of adenosine supports their hypothesis that inhibiting XO increases adenosine levels via salvage from hypoxanthine. Elevating endogenous adenosine levels by inhibiting metabolism is a well-established strategy for producing anti-nociception in many preclinical models, but inhibiting XO is likely to be particularly beneficial in some chronic pain states because of the pro-nociceptive reactive oxygen species that are produced by XO activity. Thus, allopurinol may have unexpected benefits in pain associated with chronic inflammation, diabetes and vascular dysfunction.

British Journal of Pharmacology (2009) **156**, 4–6; doi:10.1111/j.1476-5381.2008.00065.x

METODOLOGIA UTILIZADA NOS ESTUDOS EXPERIMENTAIS COM ANIMAIS

Discussão de Artigo

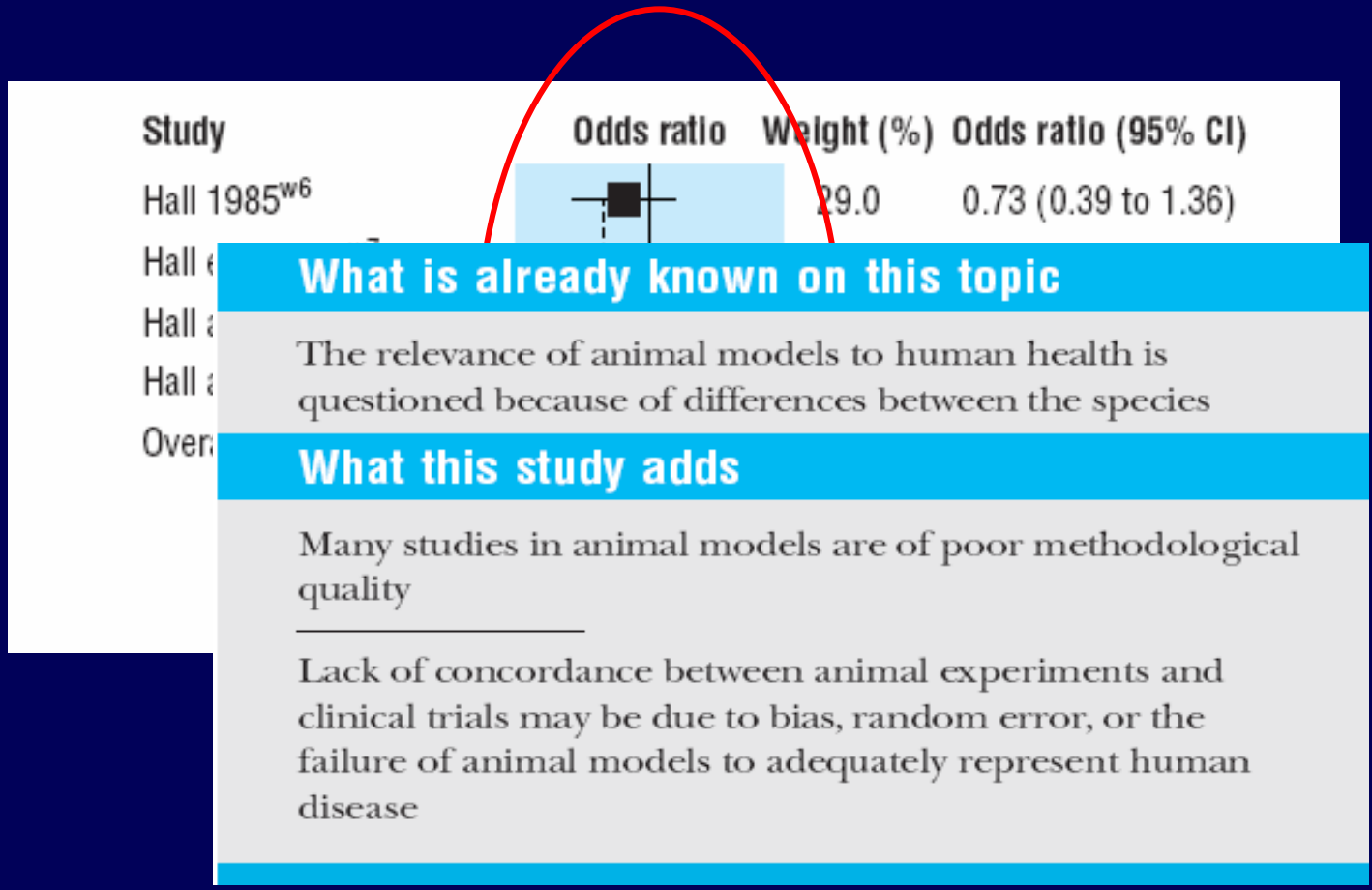
BMJ

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram and Khalid S Khan

BMJ 2007;334;197-; originally published online 15 Dec 2006; doi:10.1136/bmj.39048.407928.BE

Discussão de Artigo



Study	Odds ratio	Weight (%)	Odds ratio (95% CI)
Hall 1985[w6]		29.0	0.73 (0.39 to 1.36)
Hall			
Hall			
Hall			
Over			

What is already known on this topic

The relevance of animal models to human health is questioned because of differences between the species

What this study adds

Many studies in animal models are of poor methodological quality

---

Lack of concordance between animal experiments and clinical trials may be due to bias, random error, or the failure of animal models to adequately represent human disease

MODELOS DE DOR

TESTES TÉRMICOS

Hot-plate, Eddy e Leimback, 1953

Tail-flick, D'Amour e Smith, 1941

%MPE: 100 x (latência pós-droga – latência basal)
(Tempo de corte – latência basal)

INJEÇÃO INTRAPLANTAR DE IRRITANTES QUÍMICOS

- **Capsaicina**, 1,6 µg/pata (5 min)

  Sakurada et al., 1993

- **Glutamato**, 10 µmol/pata (15 min)

  Beirith et al., 2002

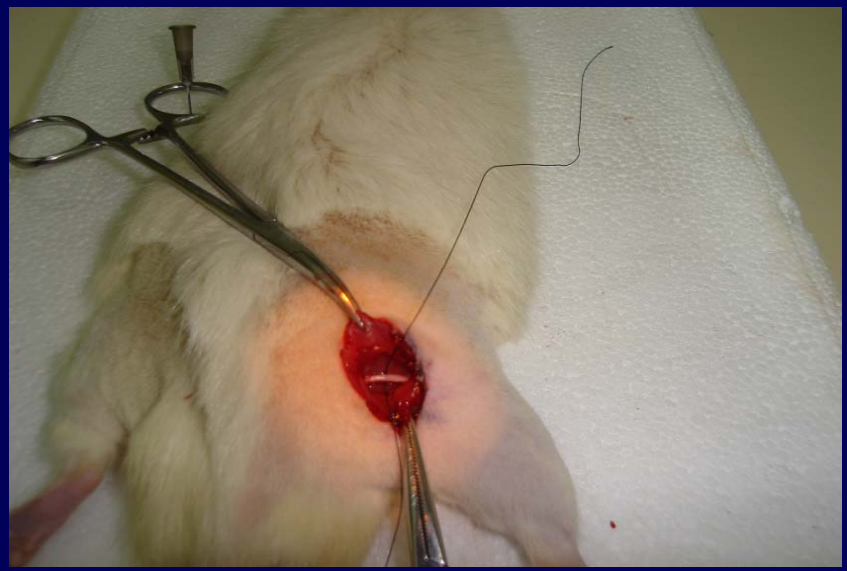
- **Formalina**, 0,92% formaldeído (2 fases – 0-5 e 15-30 min)

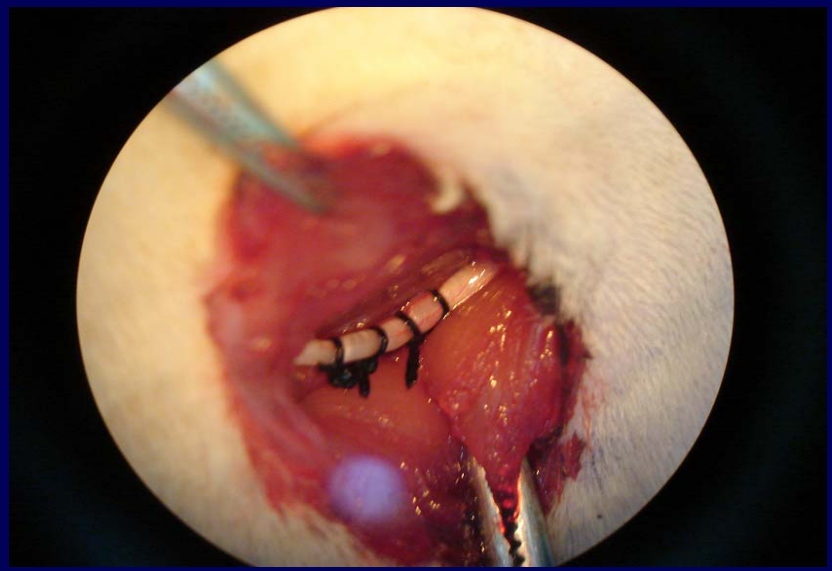
  Hunskaar e Hole, 1987

- **Ác. acético**, 1,6%, i.p. (20 min)

  Corrêa et al., 1996

TESTE PLANTAR





Bennett e Xie, Pain 1988; 33: 87-107.

Hargreaves et al., Pain 1988; 32:77-88.

REVISÃO GERAL

Sumário e Recomendações

- Dor: conceito amplo e importância epidemiológica
- Dor crônica: medidas profiláticas
- Mecanismos de dor: complexidade
  - Sistema Glutamatérgico
- Abordagem terapêutica Multimodal e Multidisciplinar
- Futuro: avaliação individual do mecanismo desencadeante da dor = tratamento guiado pela fisiopatologia
- Definição de condutas:
  - *Conhecimento da fisiopatologia*
  - *Evidências científicas sólidas*

Futuro da Pesquisa Básica em Dor com Ênfase na Fisiopatologia

- Antagonistas glutamatérgicos
- Agonistas opióides do receptor Delta
- Receptores Canabinóides (CB1 e 2)
- Receptores Histaminérgicos (H1)
- Receptores específicos de neurônios sensoriais (SNSR)
- Células Gliais e Citocinas
- Receptores Vanilóides (TRP-V1)
- Antagonistas de canais de sódio (NaV 1.8)
- Bloqueadores de Canais de Cálcio (Tipo N)
- Inibidores de Ciclooxigenase (COX 1, 2, 3)
- Cinases (MAPKinase)
- Purinas e antagonistas purinérgicos

Discussão de Artigo

The NEW ENGLAND JOURNAL of MEDICINE

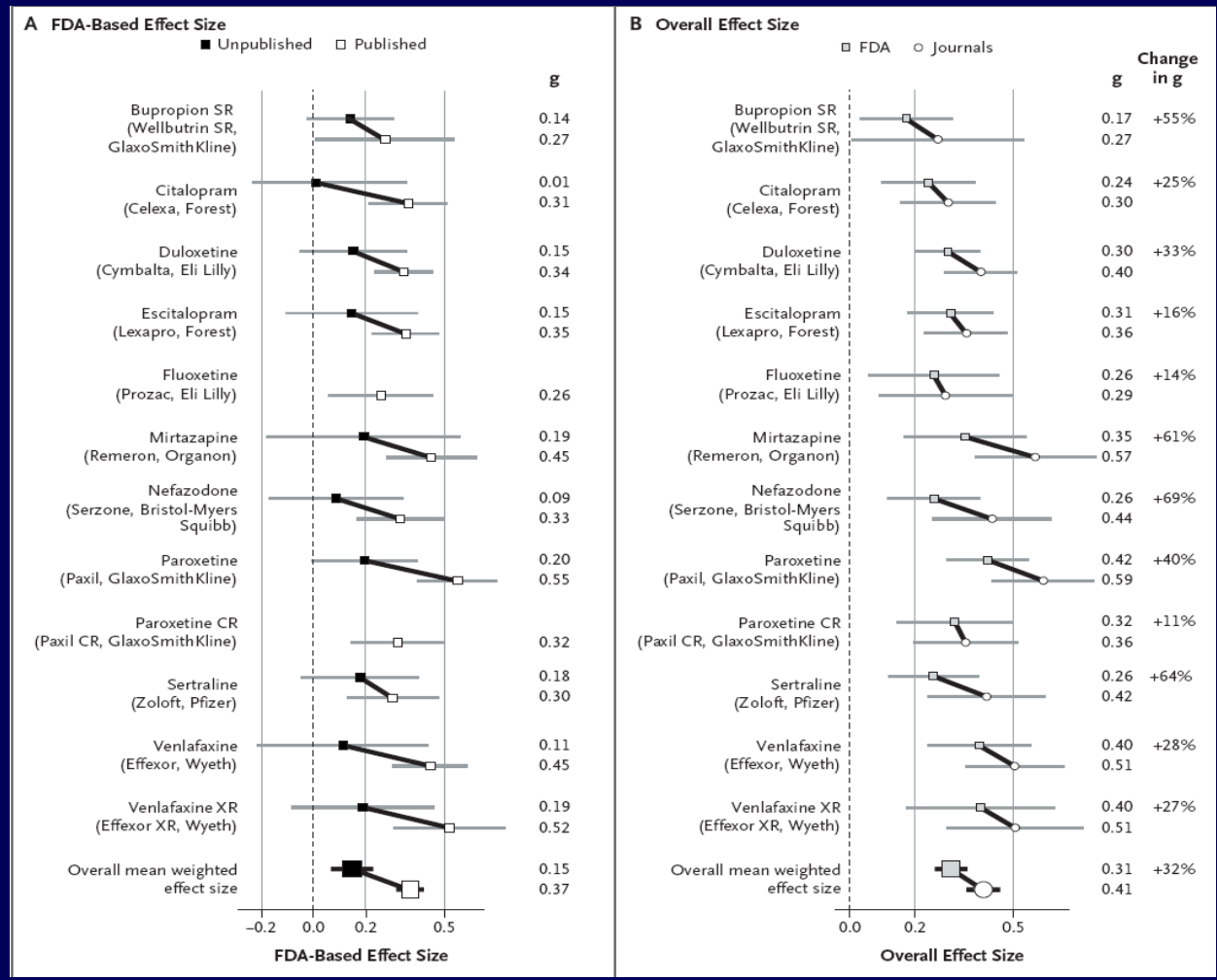
Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

N Engl J Med 2008;358:252-60.

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S.,
Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.



Estado Atual do Conhecimento

- Principais periódicos em Dor:
  - Pain
  - Anesthesiology
  - Anesthesia and Analgesia
  - Anaesthesia
  - British Journal of Anaesthesia
  - Clinical Journal of Pain
  - Pediatric Anesthesia

Referências

Artigos: PubMed – www.pubmed.com

Artigos: www.periodicos.capes.gov.br

REVISÕES SISTEMÁTICAS OU METANÁLISES

Oxford Pain Internet Site

http://www.jr2.ox.ac.uk/bandolier/booth/painpag/index.html

Cochrane Library: www.cochrane.org

Revisões: Institute's Brain Resources and Information Network (Brain):

http://www.ninds.nih.gov/

FIM