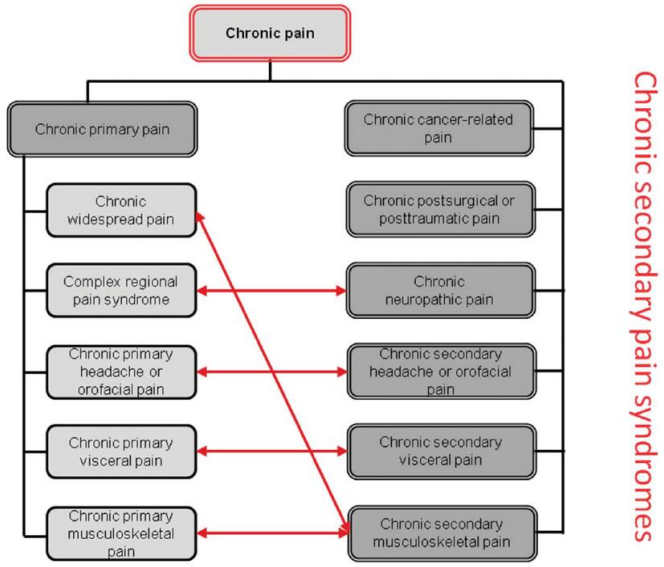
Meccanismi d’azione dei farmaci nella fibromialgia

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]



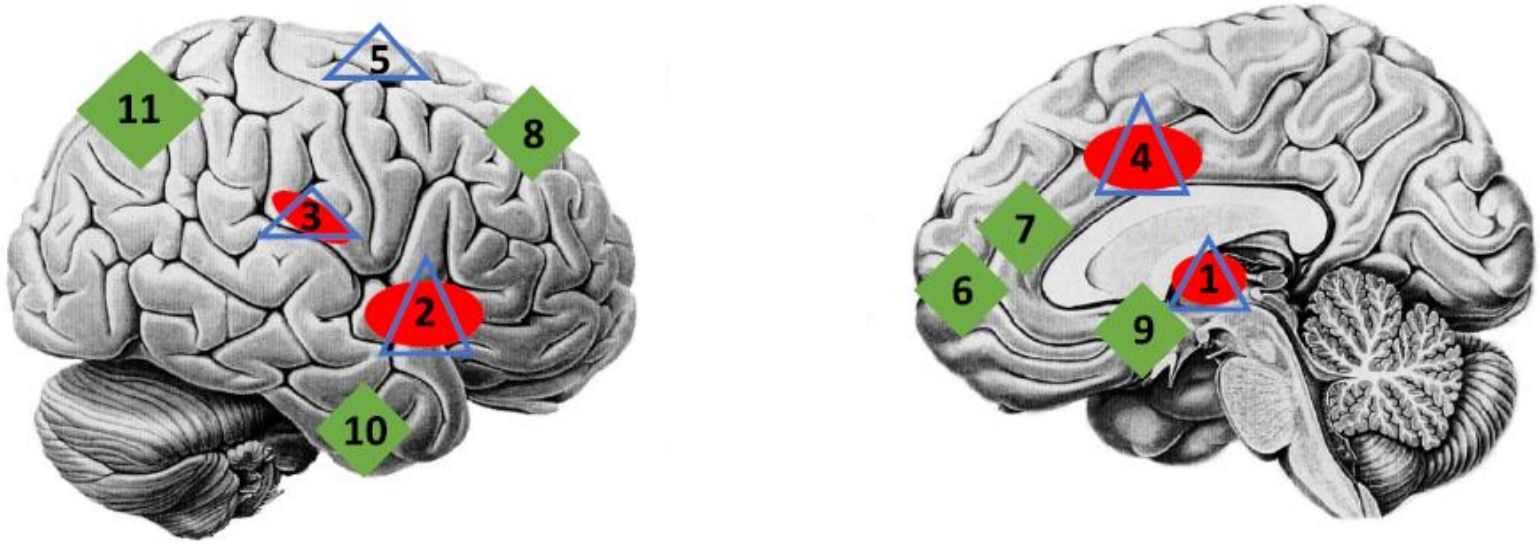
PAIN 160 (2019) 19–27

DEFINITION OF NOCIPLASTIC PAIN

Nociplastic pain is defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”

PAIN 2016;157:1382–6.

PAIN IN THE BRAIN



Acute Pain

1. thalamus
2. insula
3. SII
4. dACC

Nociceptive Pain

1. thalamus
2. insula
3. SII
4. dACC
5. SMA

Nociplastic Pain

6. mPFC
7. rACC
8. SFG
9. NAc
10. ITG
11. PPC

Fig. 1. Pain in the brain. Neural networks associated with three causally discrete types of pain: acute, nociceptive, and nociplastic. Note the high degree of overlap between the acute pain and nociceptive pain networks, which include both sensory and affective regions. In contrast, the nociplastic pain network includes relatively distinct affective regions. Abbreviations: SII, secondary somatosensory cortex; SMA, supplementary motor area; mPFC, medial prefrontal cortex; rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; SFG, superior frontal gyrus; NAc, nucleus accumbens; ITG, inferior temporal gyrus; PPC, posterior parietal cortex.

Neuroscience and Biobehavioral Reviews 135 (2022) 104558

Research Paper

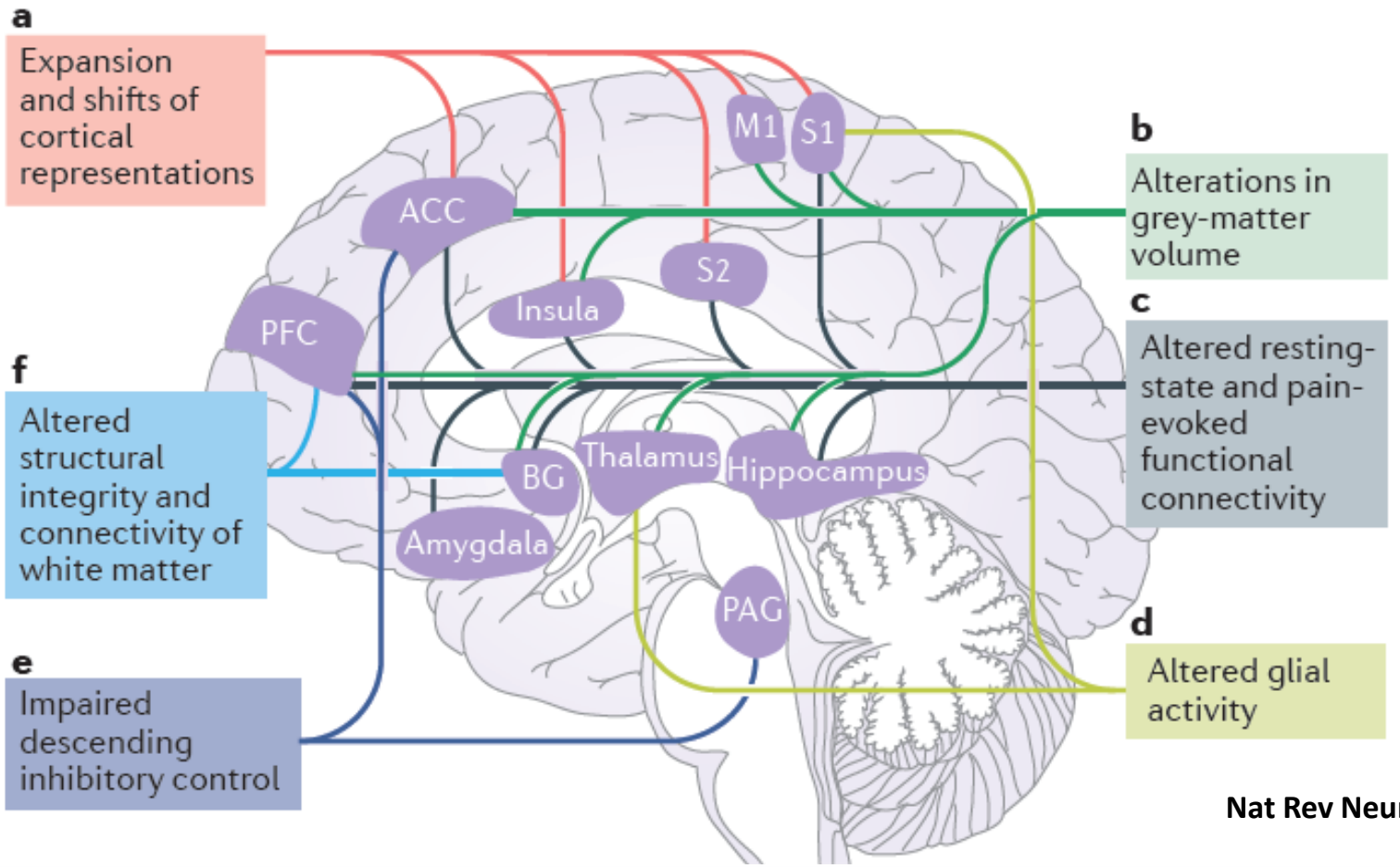
PAIN®

OPEN

Distinct aberrations in cerebral pain processing differentiating patients with fibromyalgia from patients with rheumatoid arthritis

Angelica Sandström[a,b,*], Isabel Ellerbrock[a,b], Monika Löfgren[c], Reem Altawil[d], Indre Bileviciute-Ljungar[c], Jon Lampa[d], Eva Kosek[a,b,e]

Structural and functional changes in the human brain in chronic pain conditions.



Nat Rev Neurosci 2017 Jan 20; 18 (2): 113

Table. **Pathophysiology of Fibromyalgia: Potential Mechanisms**

Mechanism	Description
Central sensitization	Amplification of pain in the spinal cord via spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain centers (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord
Neurotransmitter abnormalities	Decreased serotonin in the central nervous system may lead to aberrant pain signaling; this may partly be explained by a serotonin transporter polymorphism Decreased dopamine transmission in the brain may lead to chronic pain through unclear mechanisms
Neurohumoral abnormalities	Dysfunction in the hypothalamic–pituitary–adrenal axis, including blunted cortisol responses and lack of cortisol diurnal variation, is associated with (but is not specific for) fibromyalgia
Psychiatric comorbid conditions	Patients with fibromyalgia have increased rates of psychiatric comorbid conditions, including depression, anxiety, posttraumatic stress, and somatization; these may predispose to the development of fibromyalgia

Ann Intern Med. 2007;146:726-734.

PRINCIPAL FIBROMYALGIA SYMPTOMS

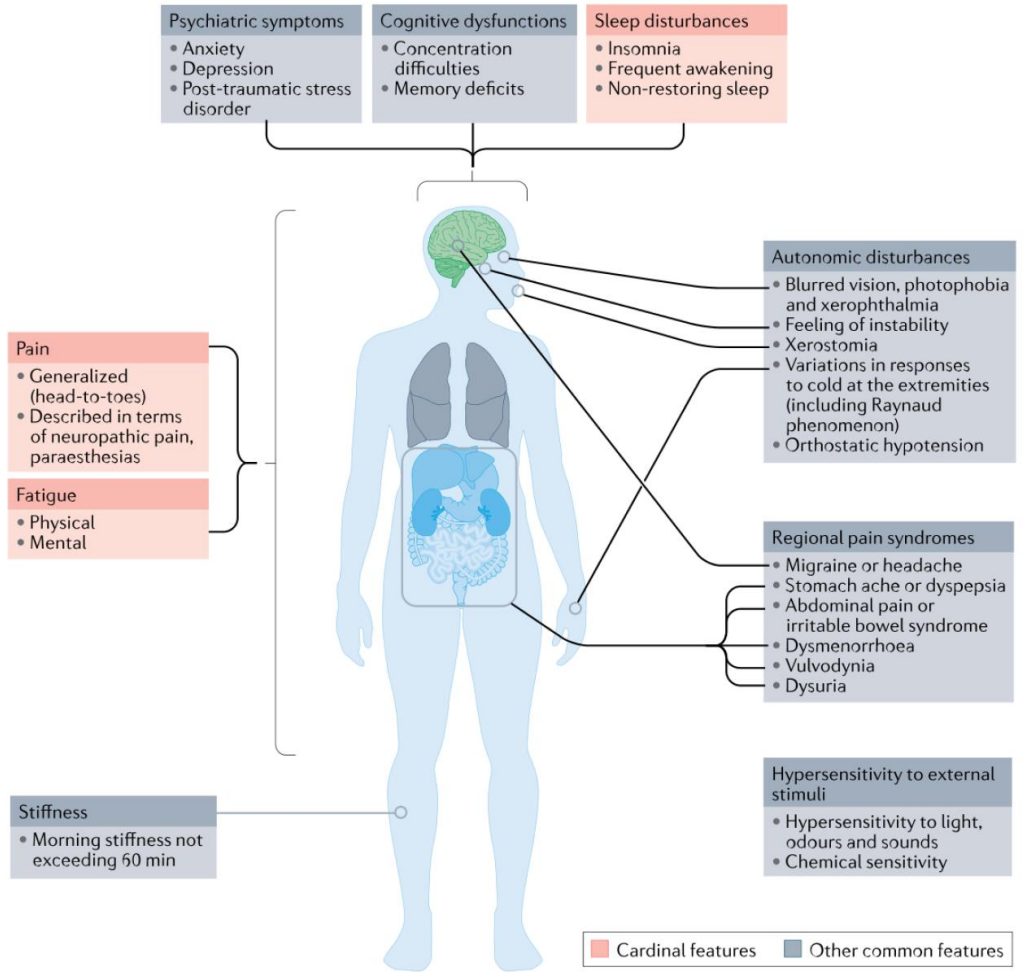
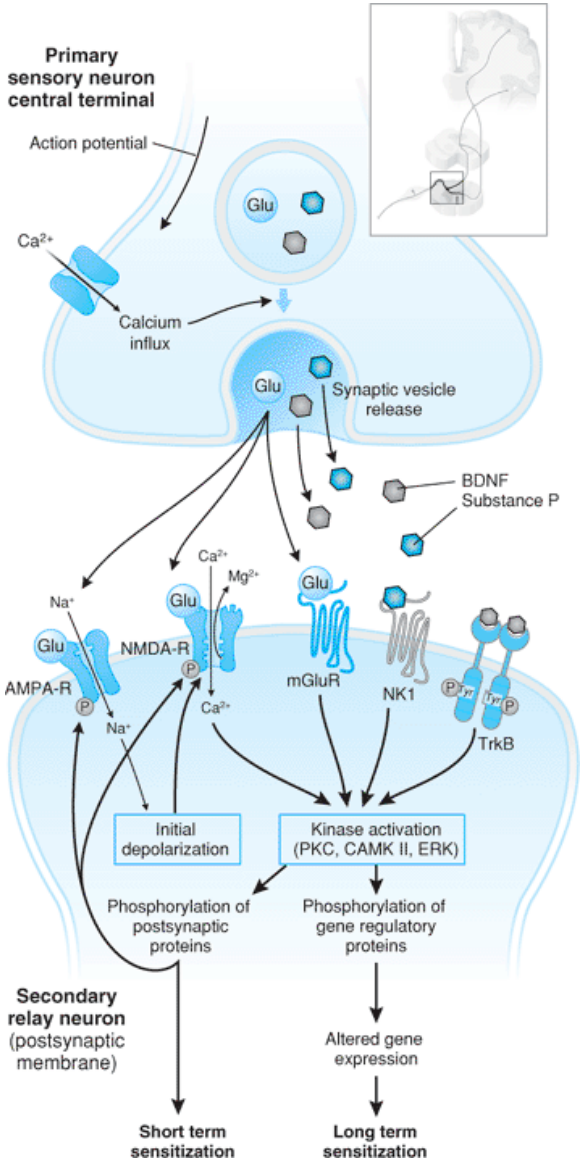


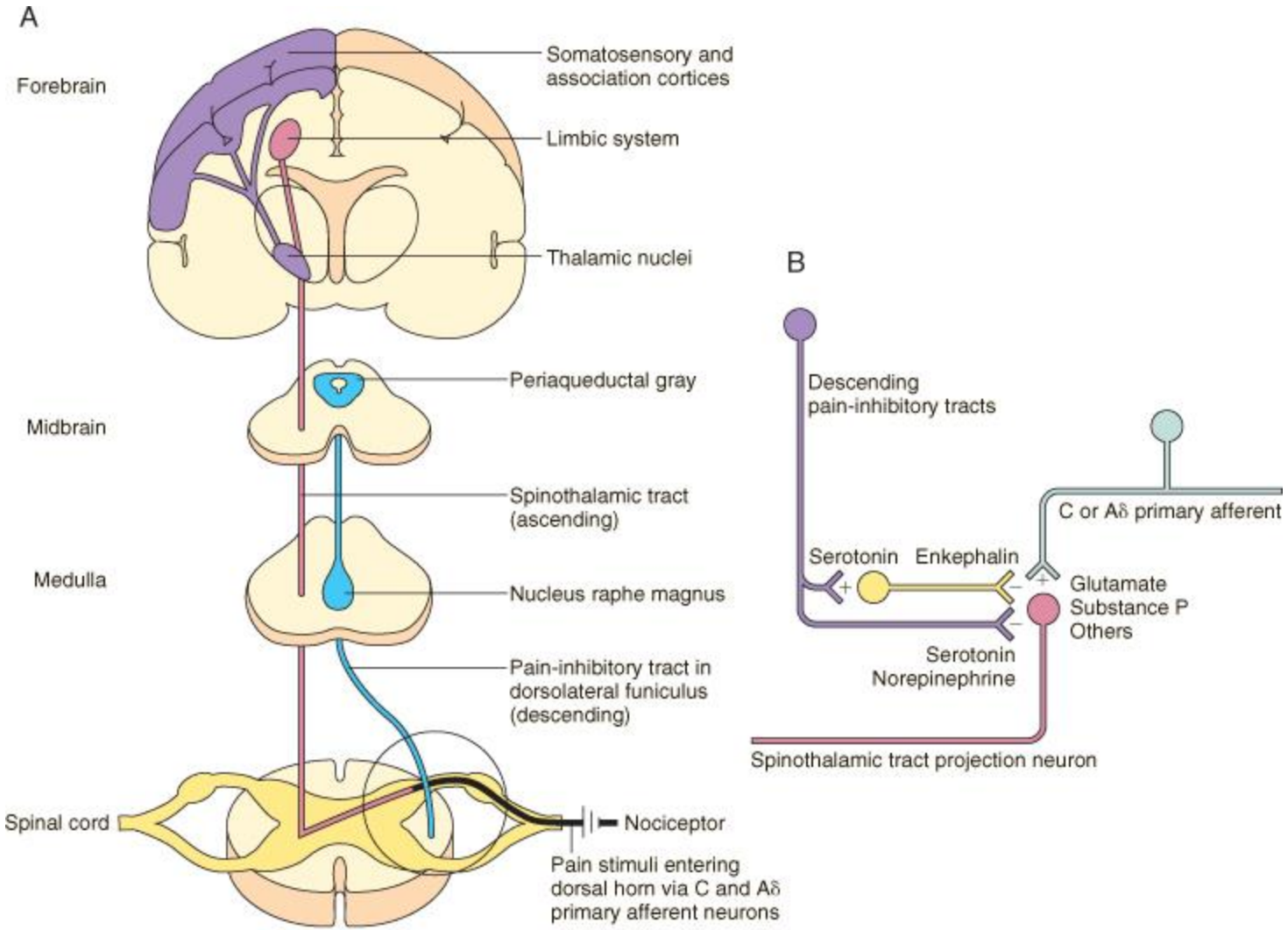
Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be are divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other common features (shown in in grey).

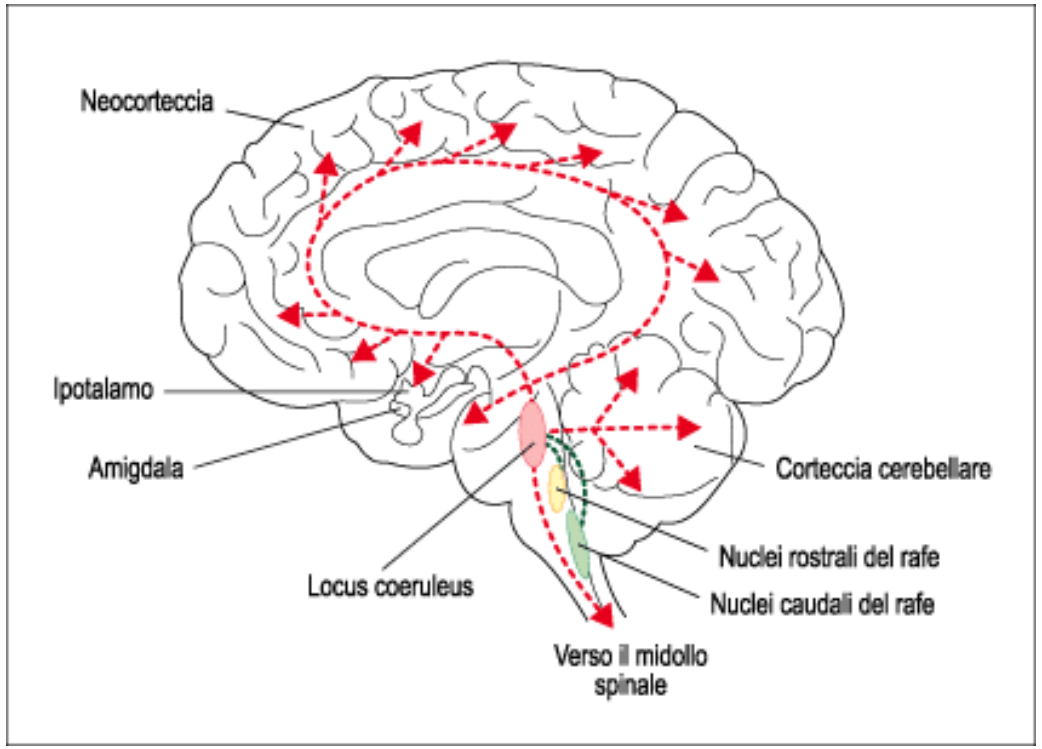
Sarzi-Puttini P *et al.* *Nature Rev Rheumatol* 2020 16: 645-660



SENSIBILIZZAZIONE SPINALE

Diego Fornasari




Neocorteccia
Ipotalamo
Amigdala
Locus coeruleus
Corteccia cerebellare
Nuclei rostrali del rafe
Nuclei caudali del rafe
Verso il midollo spinale

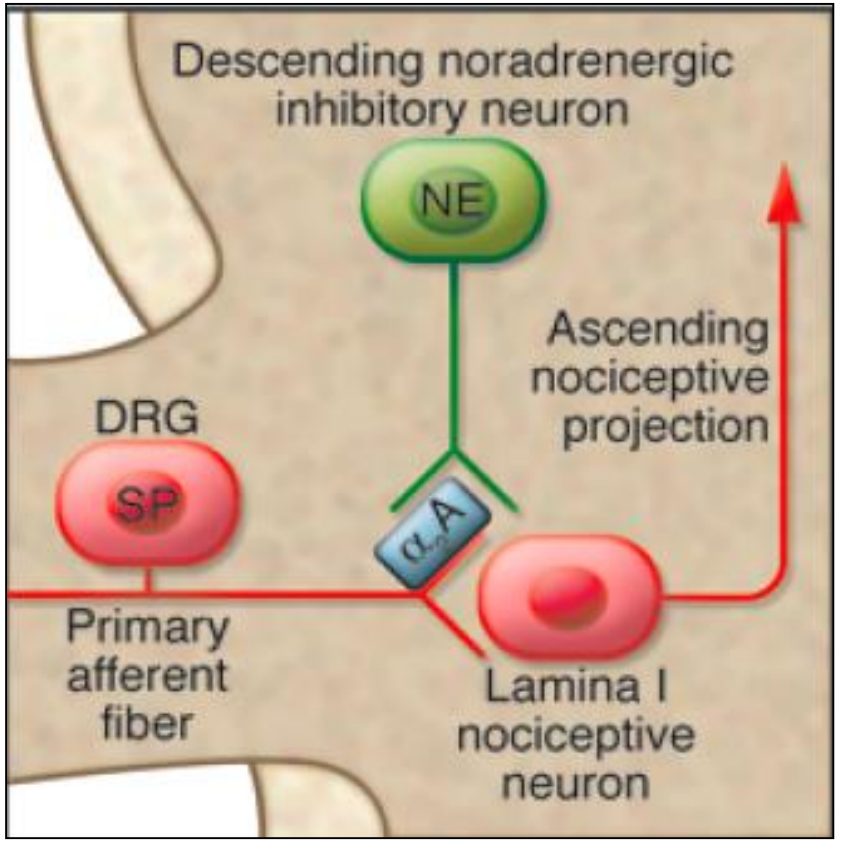
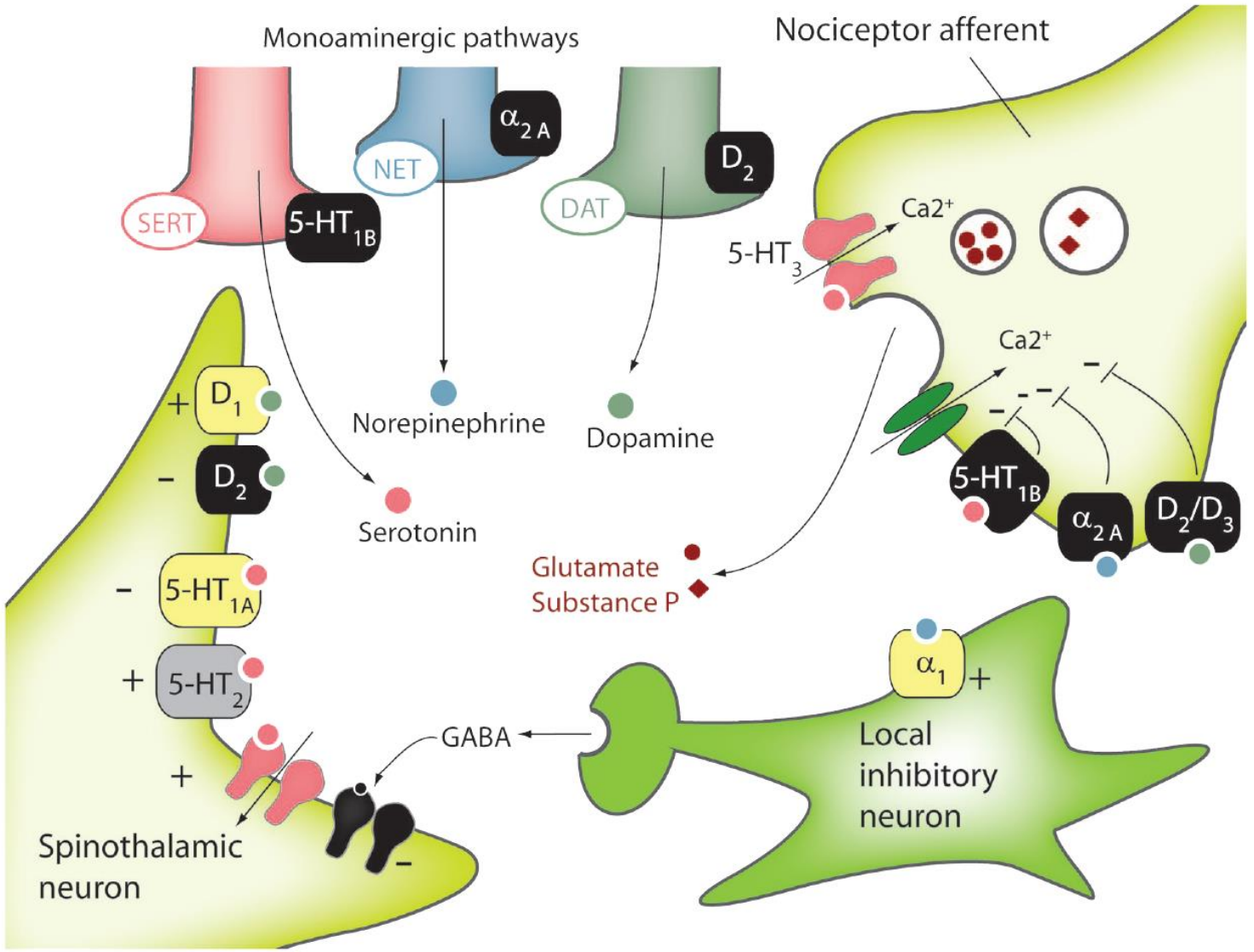
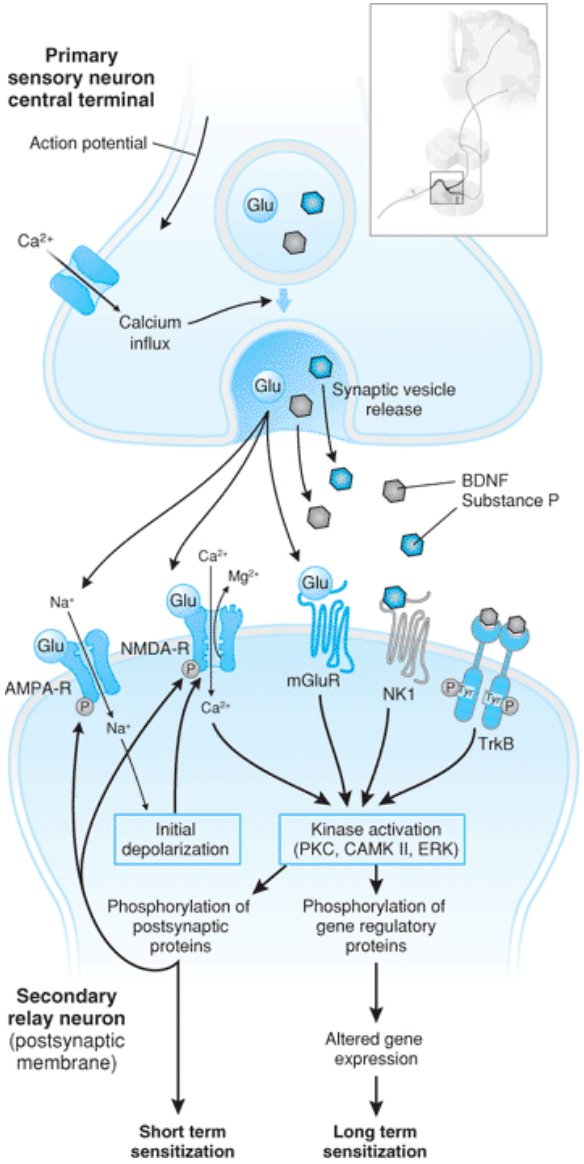

Descending noradrenergic inhibitory neuron
NE
Ascending nociceptive projection
DRG
SP
α2A
Primary afferent fiber
Lamina I nociceptive neuron

Figure 2 **Potential targets and receptor mechanism mediating the pain modulatory effects of monoamines in the dorsal horn**



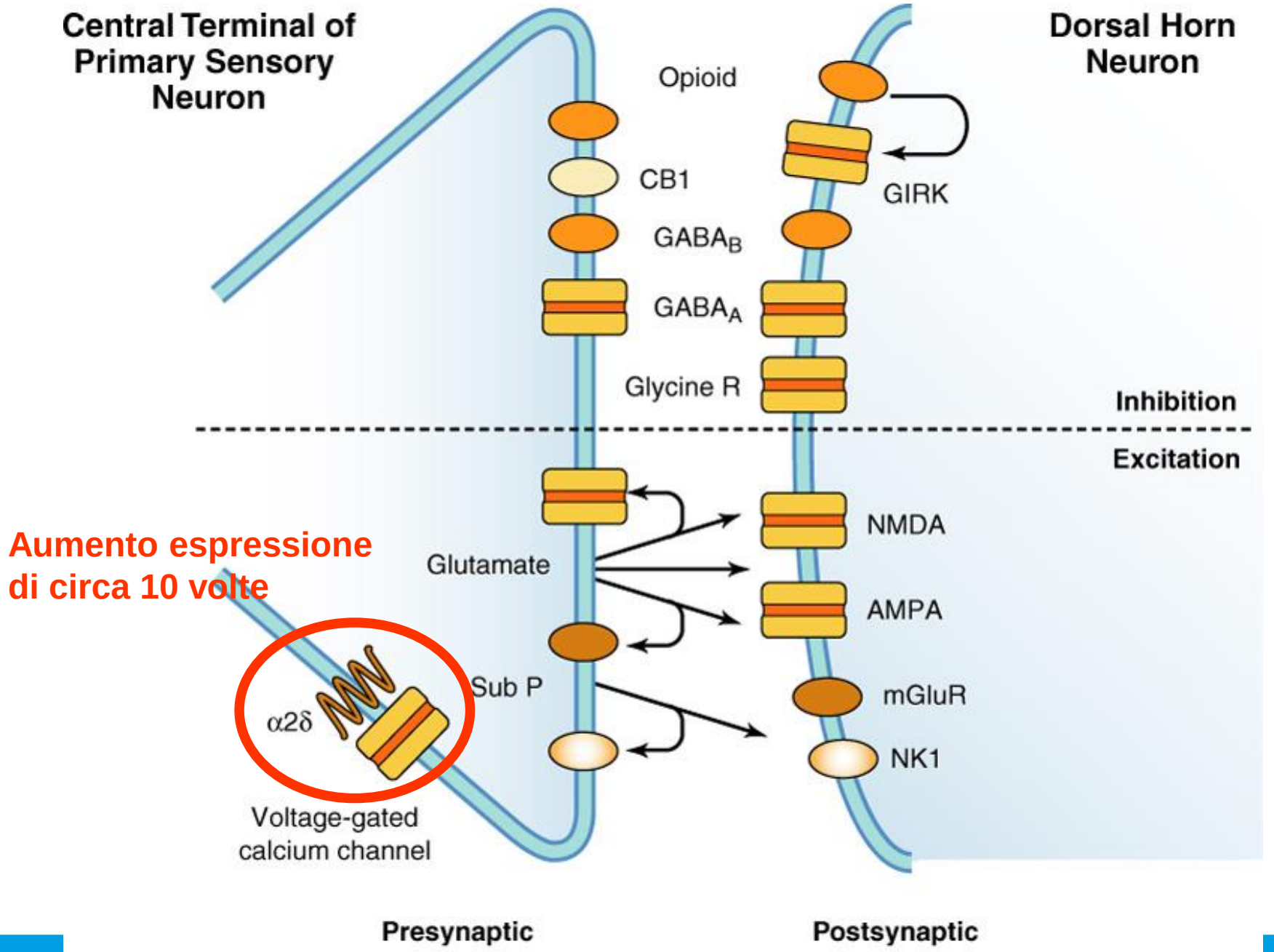
ANTIDEPRESSIVI

FARMACO	APPLICAZIONE CLINICA	REAZIONI AVVERSE	CONTROINDICAZIONI	CONSIDERAZIONI TERAPEUTICHE
IMIPRAMINA	DOLORE NEUROPATICO	CARDIOTOSSICITA'	CONCOMITANTE USO DI INIBITORI DELLE MAO, DIFETTI DI CONDUZIONE CARDIACA	
DULOXETINA	DOLORE NEUROPATICO LOW-BACK PAIN	COME IMIPRAMINA	COME IMIPRAMINA	
VENLAFAXINA	DOLORE NEUROPATICO	COME IMIPRAMINA	COME IMIPRAMINA	

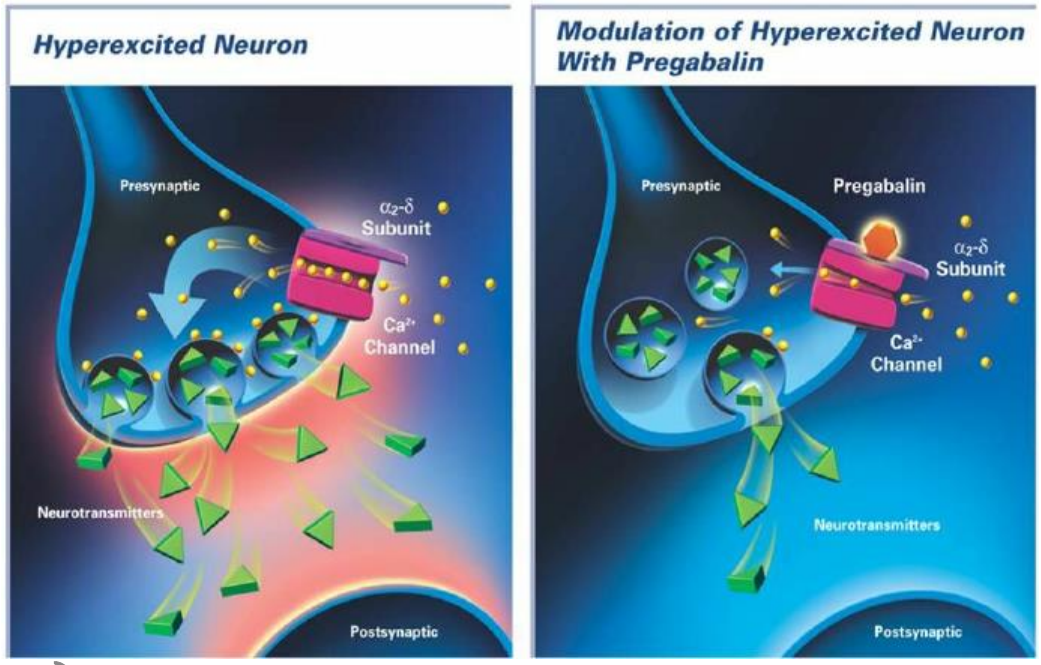


SENSIBILIZZAZIONE SPINALE

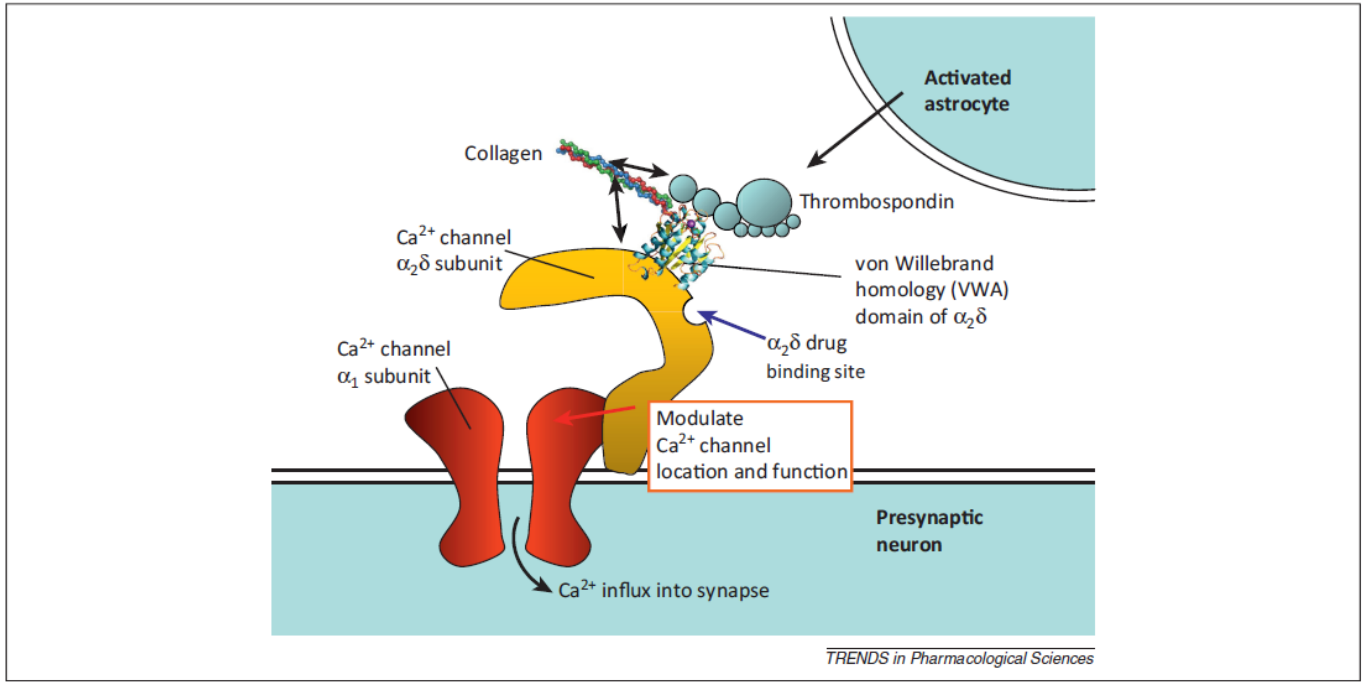
Diego Fornasari



Aumento espressione di circa 10 volte



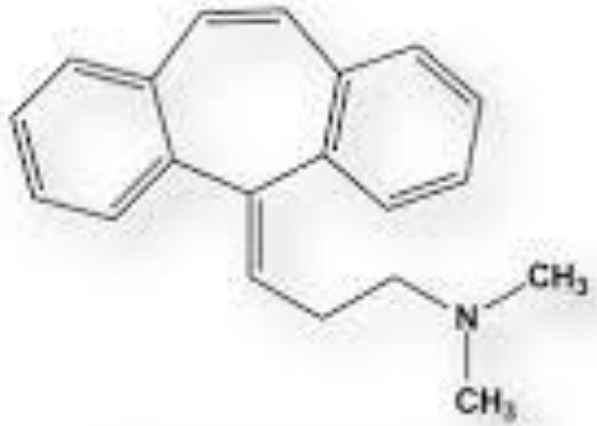
Diego Fornasari



Diego Fornasari

BLOCCANTI CANALI PER IL CALCIO (SUBUNITA' α2δ)

FARMACO	APPLICAZIONE CLINICA	REAZIONI AVVERSE	CONTROINDICAZIONI	CONSIDERAZIONI TERAPEUTICHE
GABAPENTINA	DOLORE NEUROPATICO (NEUROPATIA DIABETICA PERIFERICA DOLOROSA, NEUROPATIA POST-ERPETICA)	SONNOLENZA, VERTIGINI, FATICA. QUESTI EFFETTI, DI GRADO MODERATO, SI ESAURISCONO SPESSO DOPO 2 SETTIMANE DI TRATTAMENTO		**SCARSE INTERAZIONI FARMACOLOGICHE CON ALTRI FARMACI. NON VIENE METABOLIZZATA MA ELIMINATA CON LE URINE IMMODIFICATA**
PREGABALIN	COME GABAPENTINA	COME GABAPENTINA		**PIU' POTENTE DI GABAPENTINA SCARSE INTERAZIONI FARMACOLOGICHE CON ALTRI FARMACI. NON VIENE METABOLIZZATO MA ELIMINATO CON LE URINE IMMODIFICATA**



Ciclobenzaprina (Yurelax®)
3-(5H-dibenzo[a,d]anulen-5-iliden)-N,N-dimetilpropan-1-amina
Sinonimia:
3-(5H-dibenzo[a,d]diciclohepten-5-iliden)-N,N-dimetilpropilamina

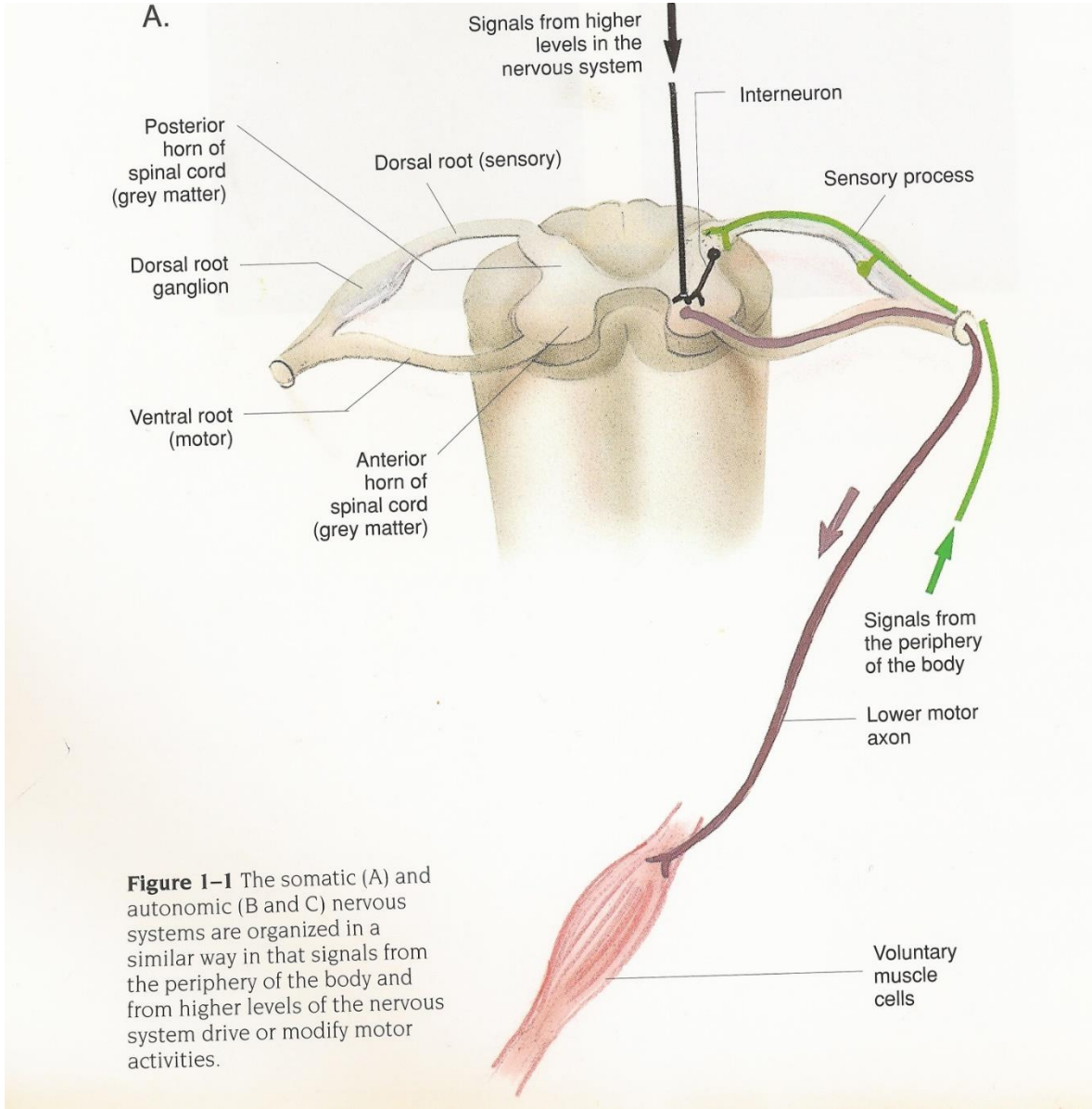


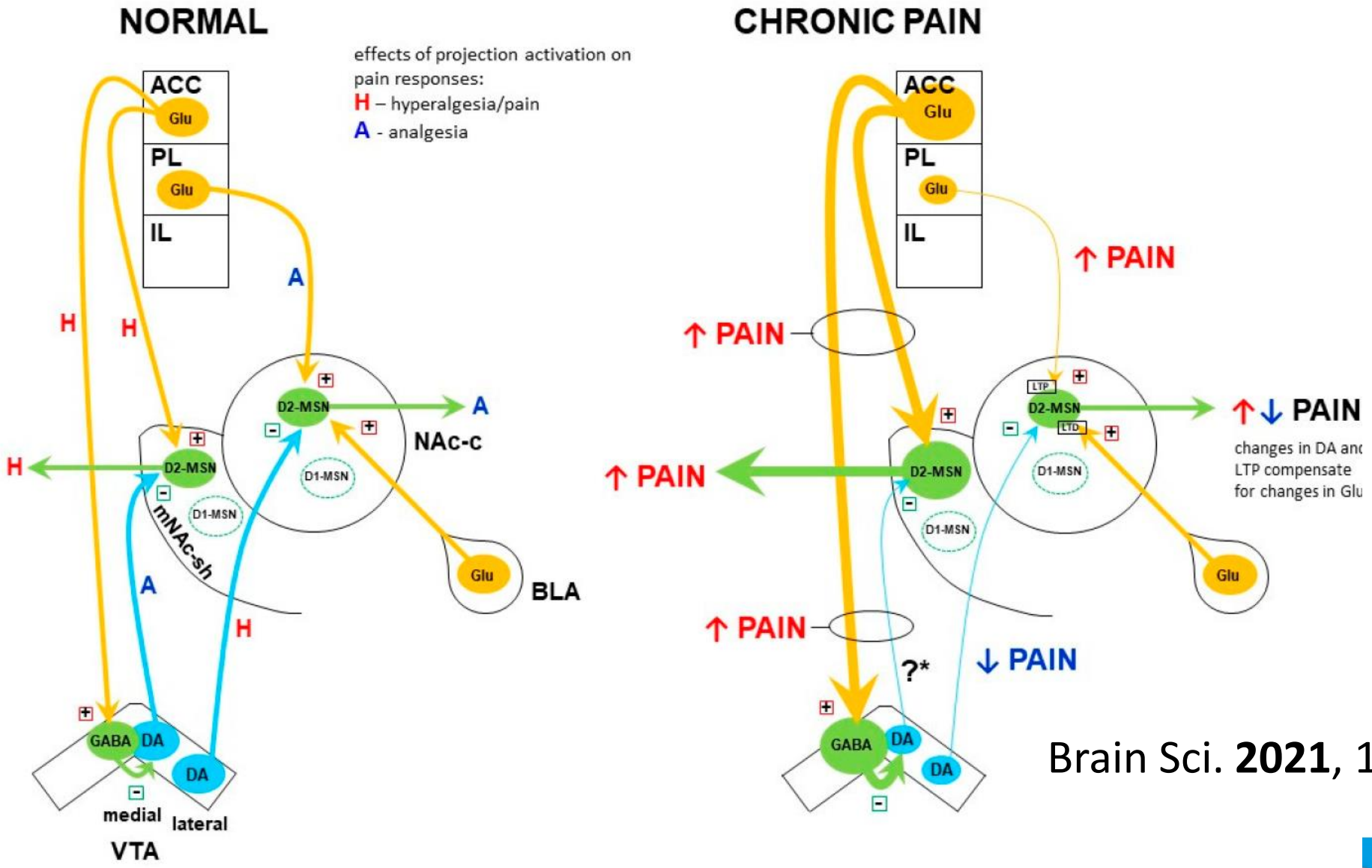
Figure 1–1 The somatic (A) and autonomic (B and C) nervous systems are organized in a similar way in that signals from the periphery of the body and from higher levels of the nervous system drive or modify motor activities.

Table. **Pathophysiology of Fibromyalgia: Potential Mechanisms**

Mechanism	Description
Central sensitization	Amplification of pain in the spinal cord via spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain centers (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord
Neurotransmitter abnormalities	Decreased serotonin in the central nervous system may lead to aberrant pain signaling; this may partly be explained by a serotonin transporter polymorphism Decreased dopamine transmission in the brain may lead to chronic pain through unclear mechanisms
Neurohumoral abnormalities	Dysfunction in the hypothalamic–pituitary–adrenal axis, including blunted cortisol responses and lack of cortisol diurnal variation, is associated with (but is not specific for) fibromyalgia
Psychiatric comorbid conditions	Patients with fibromyalgia have increased rates of psychiatric comorbid conditions, including depression, anxiety, posttraumatic stress, and somatization; these may predispose to the development of fibromyalgia

Ann Intern Med. 2007;146:726-734.

Interactions between the Ventral Mesostriatal Dopaminergic Pathway and Corticostriatal Glutamatergic Afferents in chronic pain



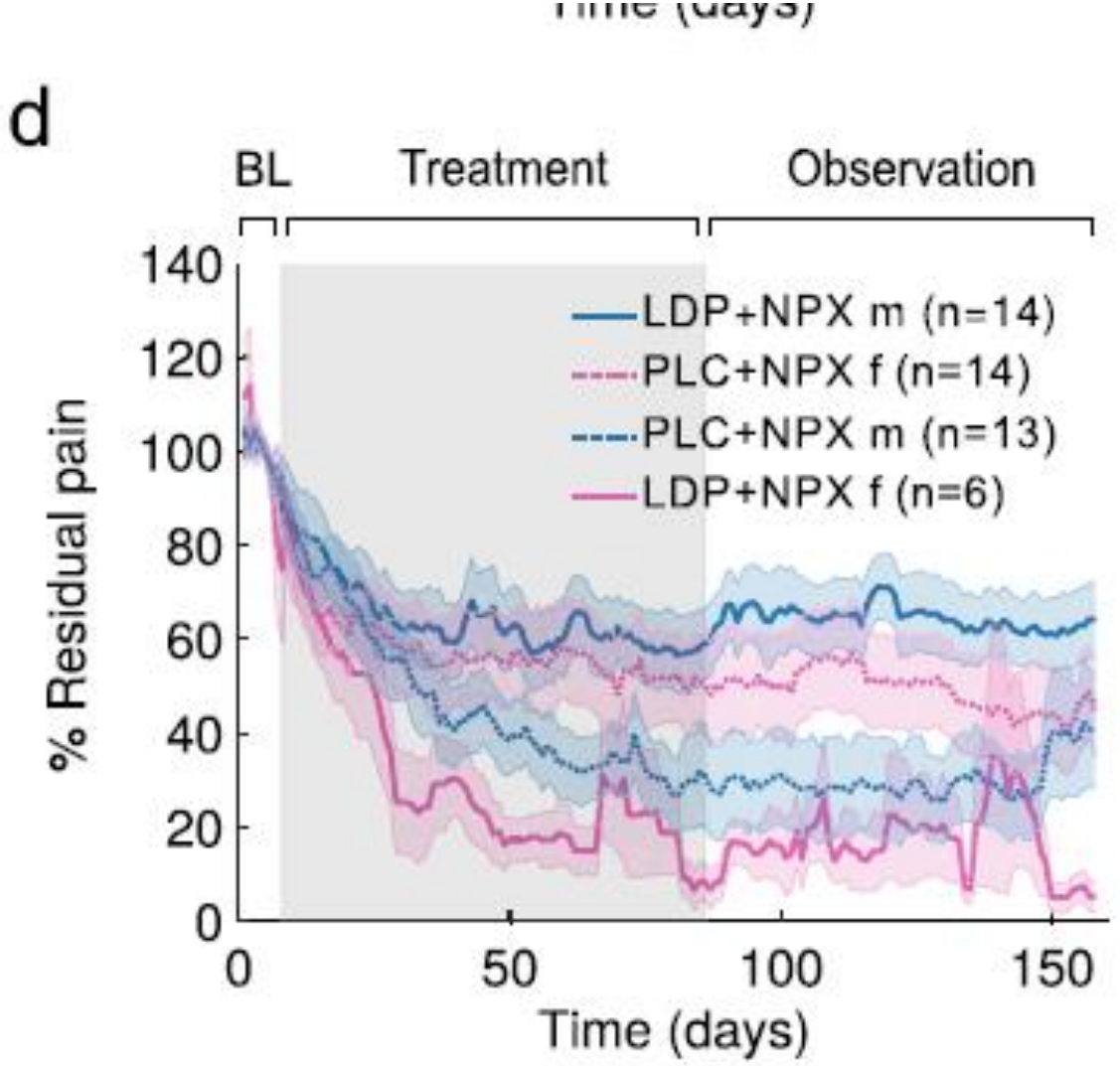
Brain Sci. **2021**, 11, 1311

Pain Ther
https://doi.org/10.1007/s40122-021-00297-2

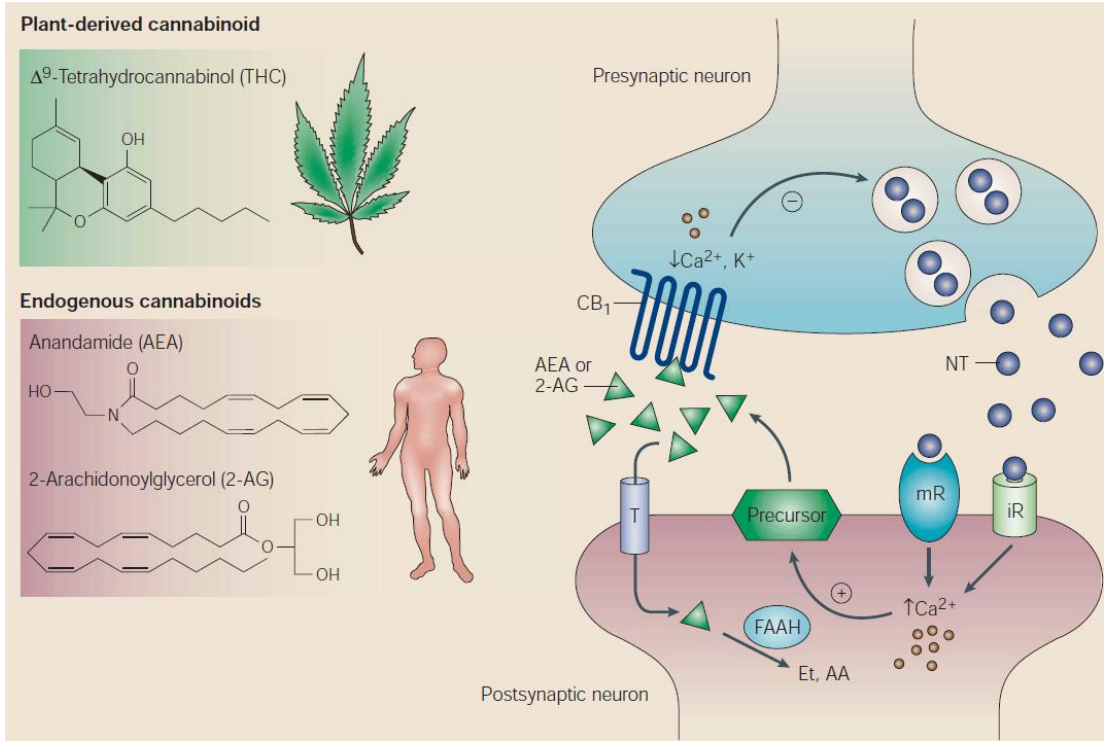
ORIGINAL RESEARCH

Sex-Specific Pharmacotherapy for Back Pain: A Proof-of-Concept Randomized Trial

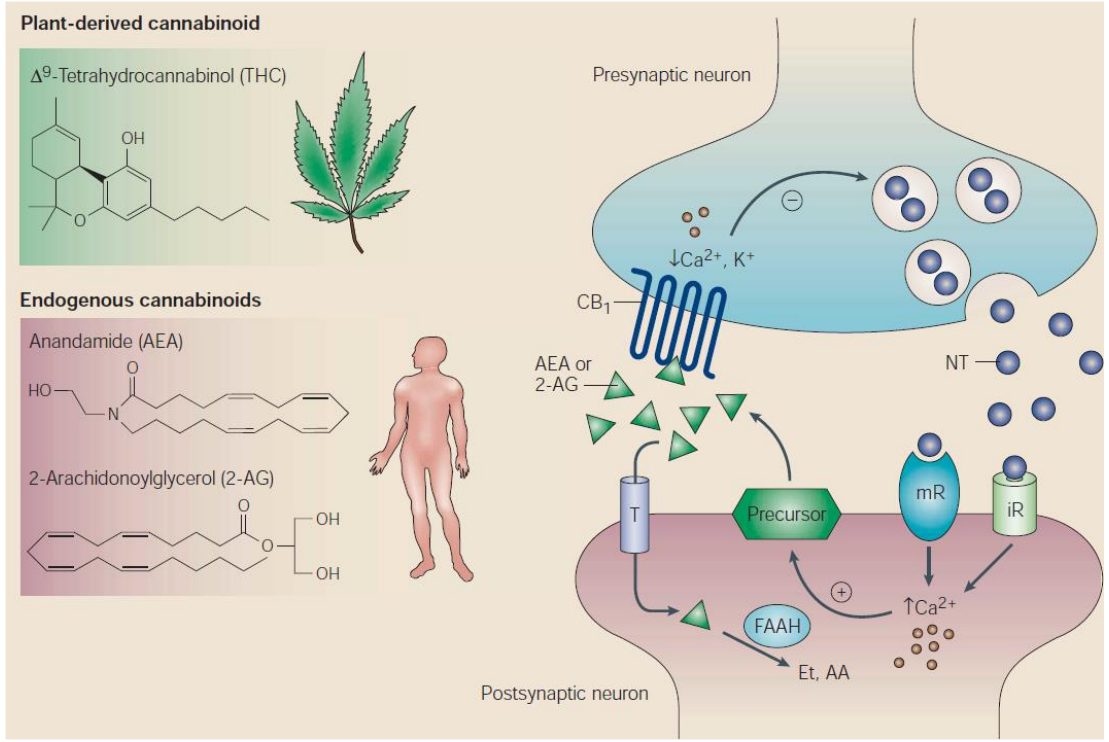
Diane Reckziegel · Pascal Tétreault · Mariam Ghantous · Kenta Wakaizumi · Bogdan Petre · Lejian Huang · Rami Jabakhanji · Taha Abdullah · Etienne Vachon-Presseau · Sara Berger · Alexis Baria · James W. Griffith · Marwan N. Baliki · Thomas J. Schnitzer · A. Vania Apkarian


d
BL
Treatment
Observation
LDP+NPX m (n=14)
PLC+NPX f (n=14)
PLC+NPX m (n=13)
LDP+NPX f (n=6)
% Residual pain
0
20
40
60
80
100
120
140
0
50
100
150
Time (days)

Systematic Review and Meta-analysis Seem to Indicate that Cannabinoids for Chronic Primary Pain Treatment Have Limited Benefit



Giossi R, Carrara F, Padroni M, Bilancio MC, Mazzari M, Enisci S, Romio MS, Boni G, Corrù F, Fittipaldo VA, Tramacere I, Pani A, Scaglione F, **Fornasari D.** **Pain Ther. 2022** Sep 21. doi: 10.1007/s40122-022-00434-5. Online ahead of print.PMID: 36129666



Key Summary Points

Chronic primary pain (CPP) is a new ICD-11 diagnostic definition including several painful conditions such as fibromyalgia, chronic regional pain syndrome, irritable bowel syndrome, and chronic migraine among others.

While interest in the potential role of cannabinoids in painful conditions has increased and previous systematic reviews found they are effective in treatment of chronic, especially secondary, non-cancer pain, limited evidence is available on the effects of cannabinoids on CPP and for this reason we performed a systematic review and a meta-analysis to evaluate the role of cannabinoids in CPP.

We found limited benefit of cannabinoids compared to placebo on pain relief in patients with CPP in the overall analysis, while we observed a significant reduction of pain in clinical trials with a long-term treatment.

Cannabinoids might improve pain and quality of life in patients with fibromyalgia.

The quality of the available evidence for cannabinoids use in CPP is generally low and future, long-term trials are needed.

MAYO CLINIC: TRATTAMENTO NEL DOLORE NEUROPATICO

Trattamenti di 1° linea

orali

Anticonvulsants			
Gabapentin[b]	300 mg at bedtime, increase every 4-7 d by 300-mg increments initially to 3 times daily, then to goal of 1800 mg/d as necessary to 3600 mg/d	3600 mg/ d (split TID)
Pregabalin[b]	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split BID)
Antidepressants			
Amitriptyline, nortriptyline[b]	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d
Duloxetine[b]	20-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split BID)
Supplements			
α-Lipoic acid	600 mg once daily	600 mg/d
Acetyl-L-carnitine	1000 mg 3 times per day	3000 mg/d (split TID)
Capsaicin (8%) patch	Should be placed by medical staff trained in its usage using nonlatex gloves; pretreat area with 4% topical lidocaine for 60 min, confirm anesthesia, apply patch(es) to affected area (may cut to shape) for 60 min, wipe clean with provided soap	4 patches per application

Fra i trattamenti di PRIMA LINEA è raccomandata:

❖**ALC 3 g/die (negli US non è disponibile ALC im)**

 ■ Mayo Clin Proc. 2015;90(7):940-951

Pharmacological Research 173 (2021) 105874

Contents lists available at ScienceDirect

Pharmacological Research

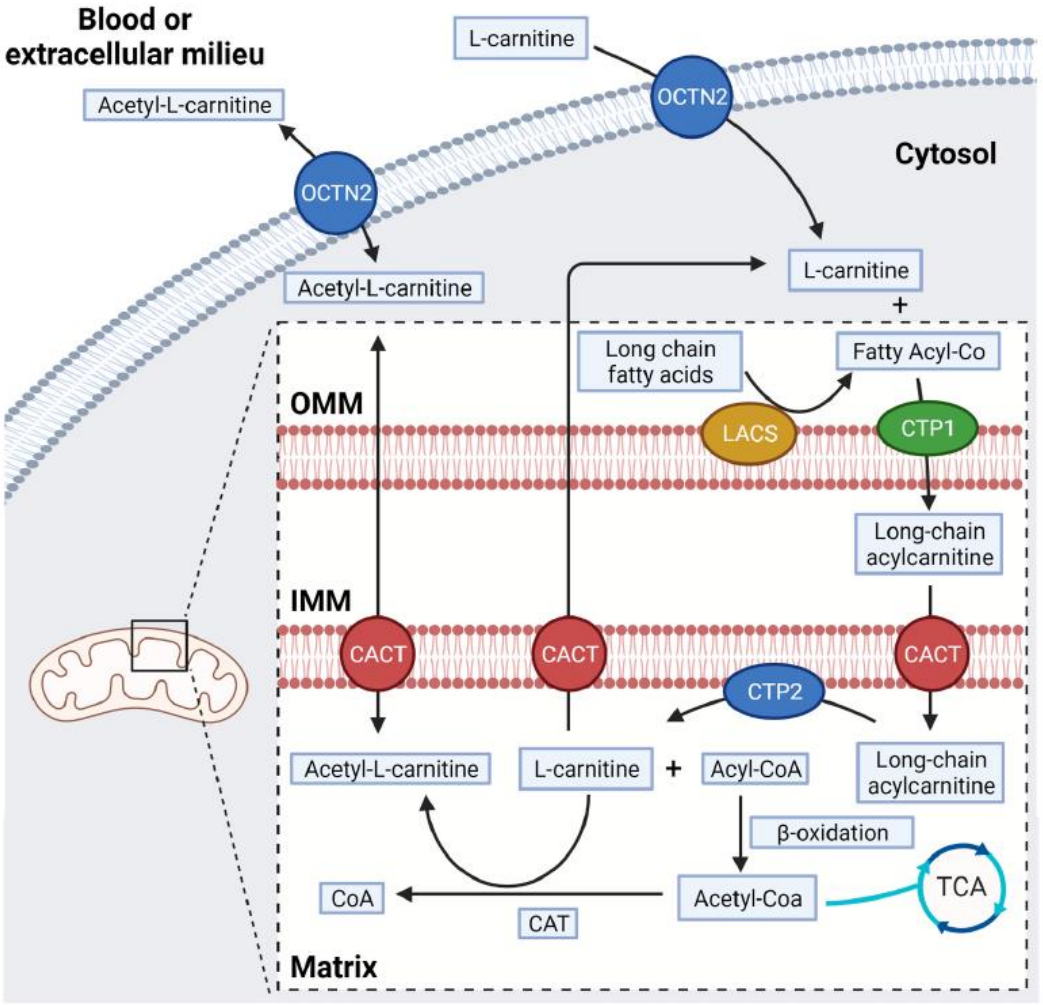
journal homepage: www.elsevier.com/locate/yphrs

Review

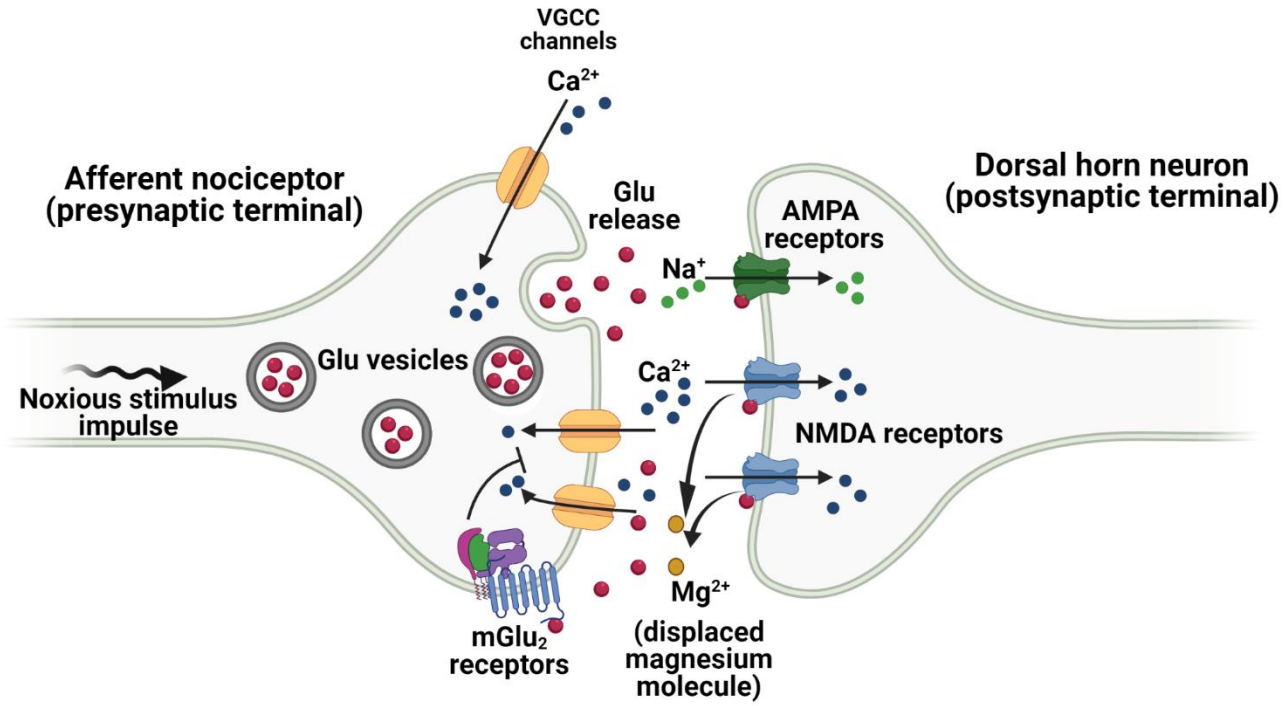
Acetyl-L-carnitine in chronic pain: A narrative review

Piercarlo Sarzi-Puttini [a], Valeria Giorgi [a,*], Simona Di Lascio [b], Diego Fornasari [b]

[a] *Rheumatology Unit, ASST Fatebenefratelli Luigi Sacco University Hospital, Milan, Italy*
[b] *Department of Medical Biotechnology and Molecular Medicine, Università degli Studi di Milano, Milan, Italy*

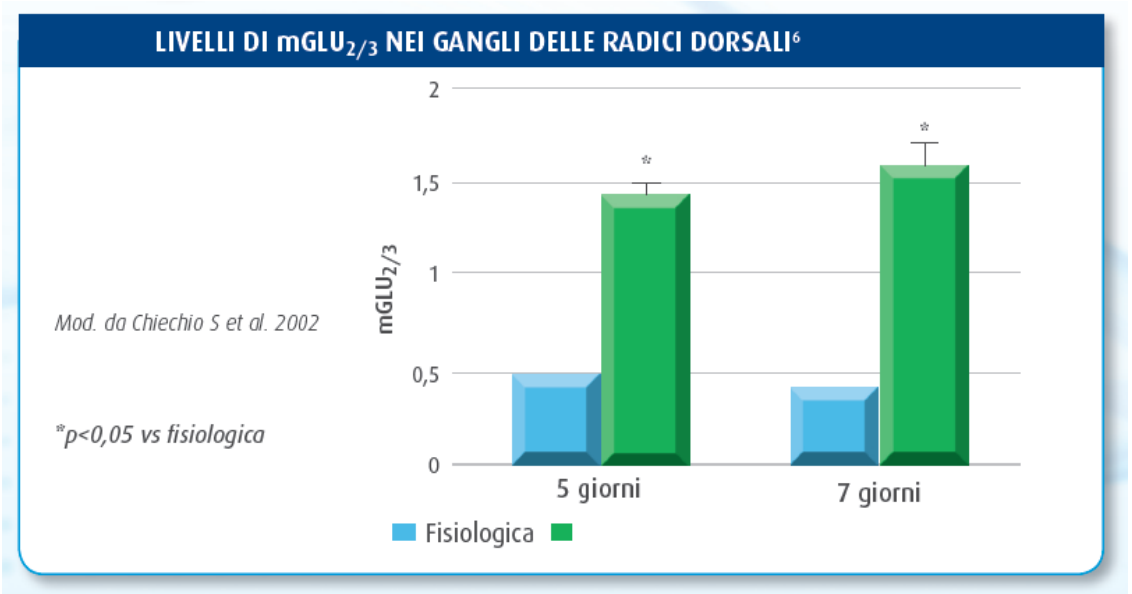


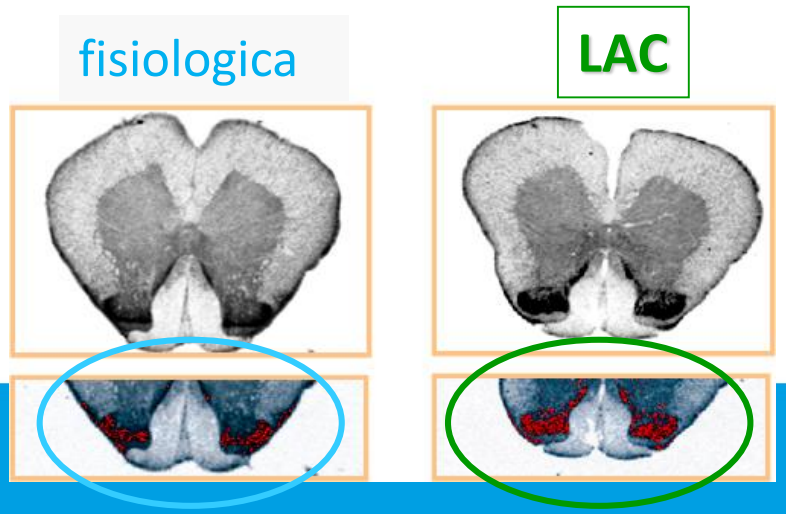
Pharmacol Res. 2021 Nov;173:105874.



Pharmacol Res. 2021 Nov;173:105874.

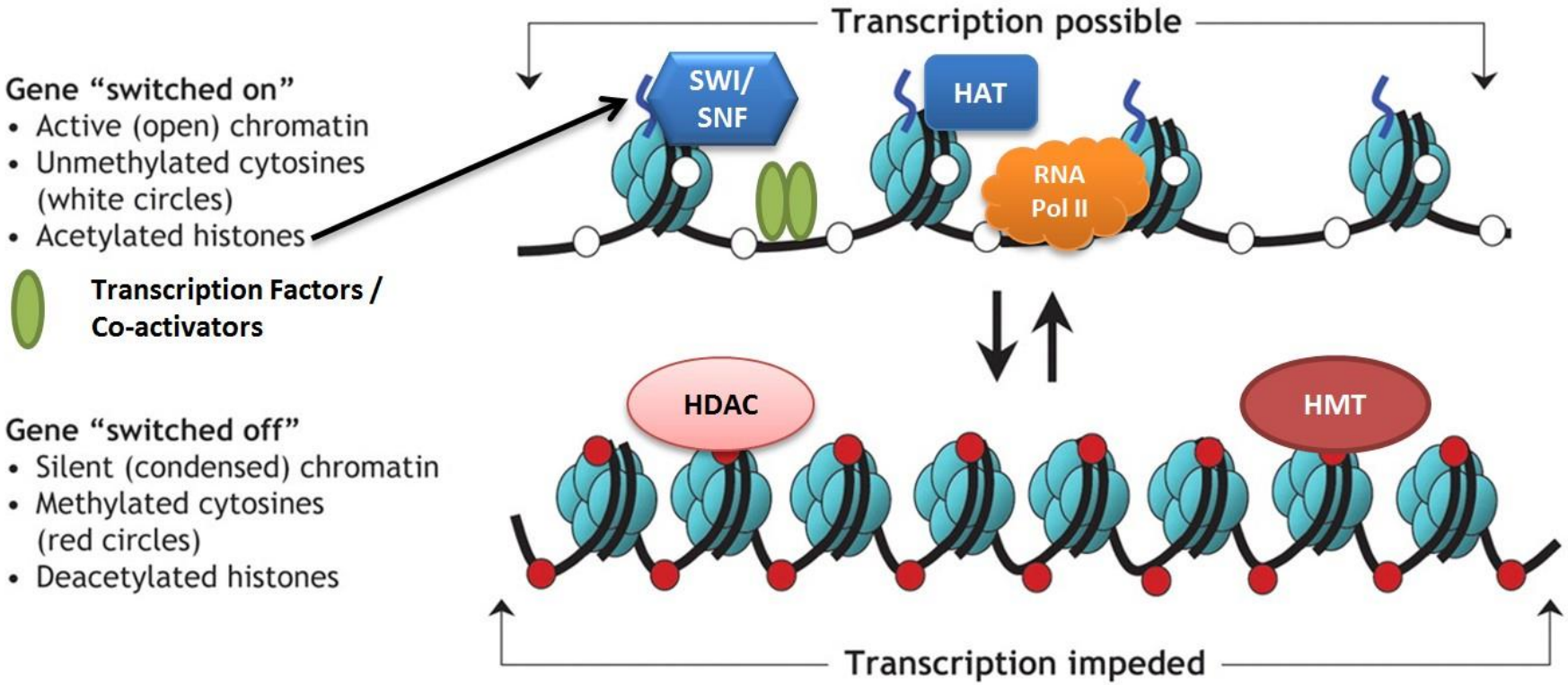
Effetto di LAC sull'espressione del recettore mGLU-2 nelle corna dorsali del midollo

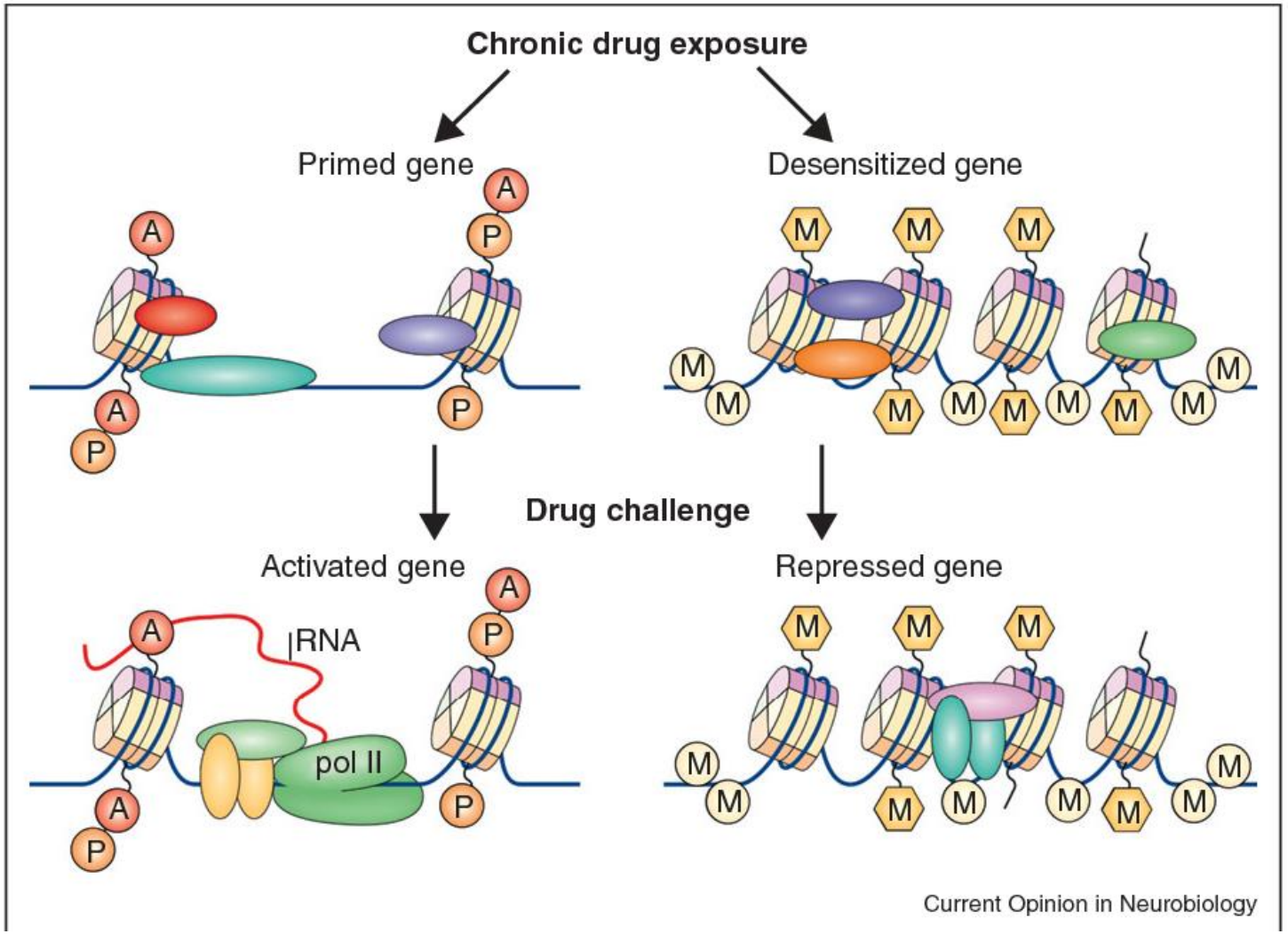




Aumento della densità di recettori mGlu-2 indotta da LAC sulle corna posteriori del midollo spinale

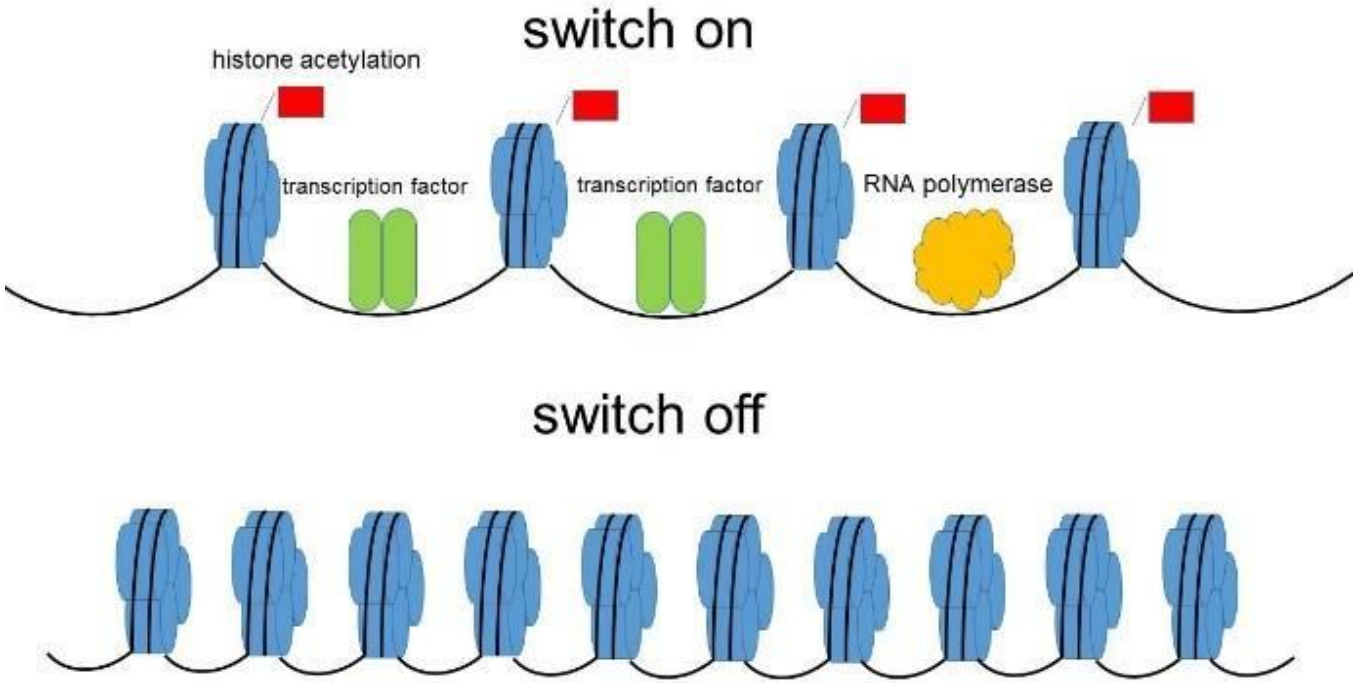
Mol Pharmacol. 2002 May;61(5):989-96.


Transcription possible
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Transcription Factors / Co-activators
SWI/ SNF
HAT
RNA Pol II
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
HDAC
HMT
Transcription impeded

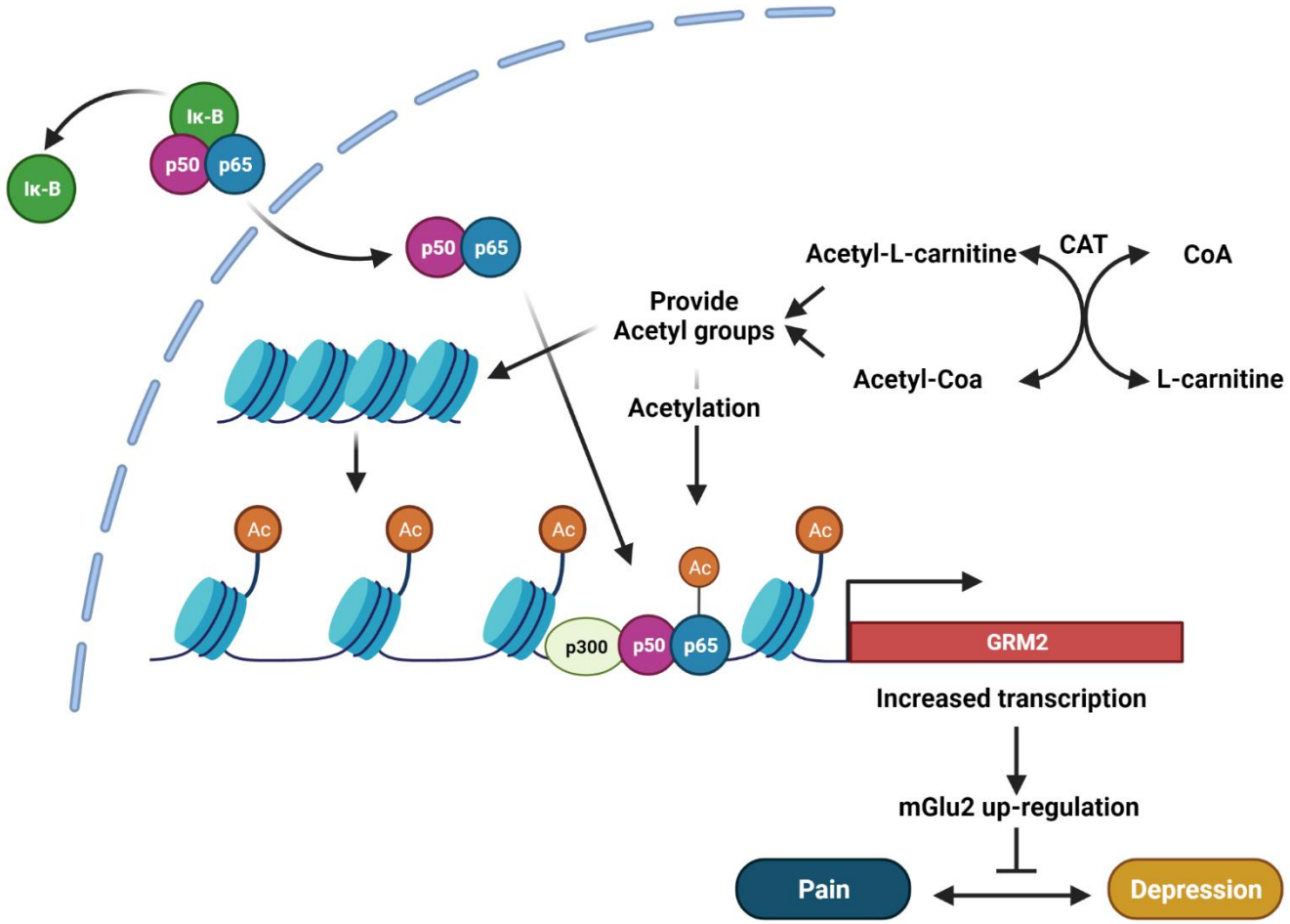

Chronic drug exposure
Primed gene
Desensitized gene
A
P
M
Drug challenge
Activated gene
Repressed gene
RNA
pol II
Current Opinion in Neurobiology

L-ACETIL-CARNITINA: donatore di gruppi acetilici

LAC regola l'espressione di geni **↑ mGlu2, ↑ Fattori di crescita nervosa, ↑ SOD**



mGLU2	→	**azione analgesica**
Fattori di crescita nervosa	→	**azione neurotrofica**
SOD (Superossidodismutasi)	→	**azione antiossidante/neuroprotettiva**



Pharmacol Res. 2021 Nov;173:105874.

L'Azione analgesica di LAC perdura oltre il termine del trattamento

Research Article

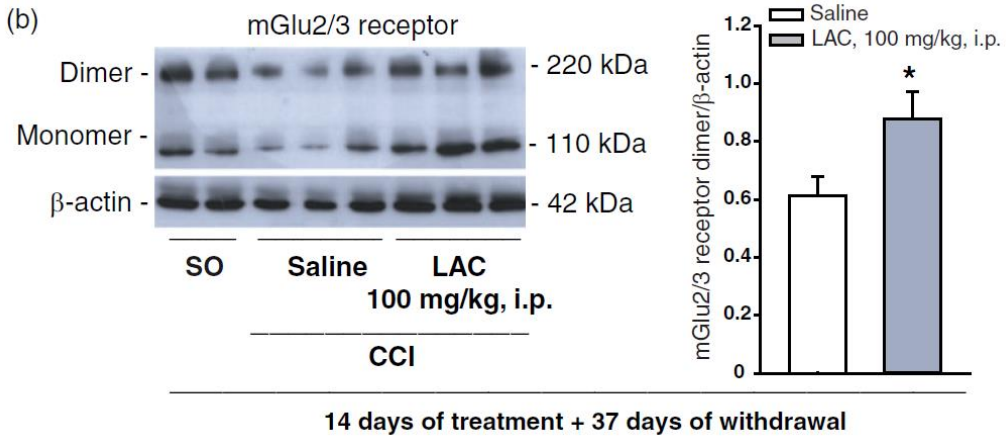
MOLECULAR PAIN

Molecular Pain
Volume 13: 1–12

DOI: 10.1177/1744806917697009
journals.sagepub.com/home/mpx
SAGE

Analgesia induced by the epigenetic drug, L-acetylcarnitine, outlasts the end of treatment in mouse models of chronic inflammatory and neuropathic pain

Serena Notartomaso[1], Giada Mascio[1], Matteo Bernabucci[1], Cristina Zappulla[1], Pamela Scarselli[1], Milena Cannella[1], Tiziana Imbriglio[1], Roberto Gradini[1,2], Giuseppe Battaglia[1], Valeria Bruno[1,3] and Ferdinando Nicoletti[1,3]

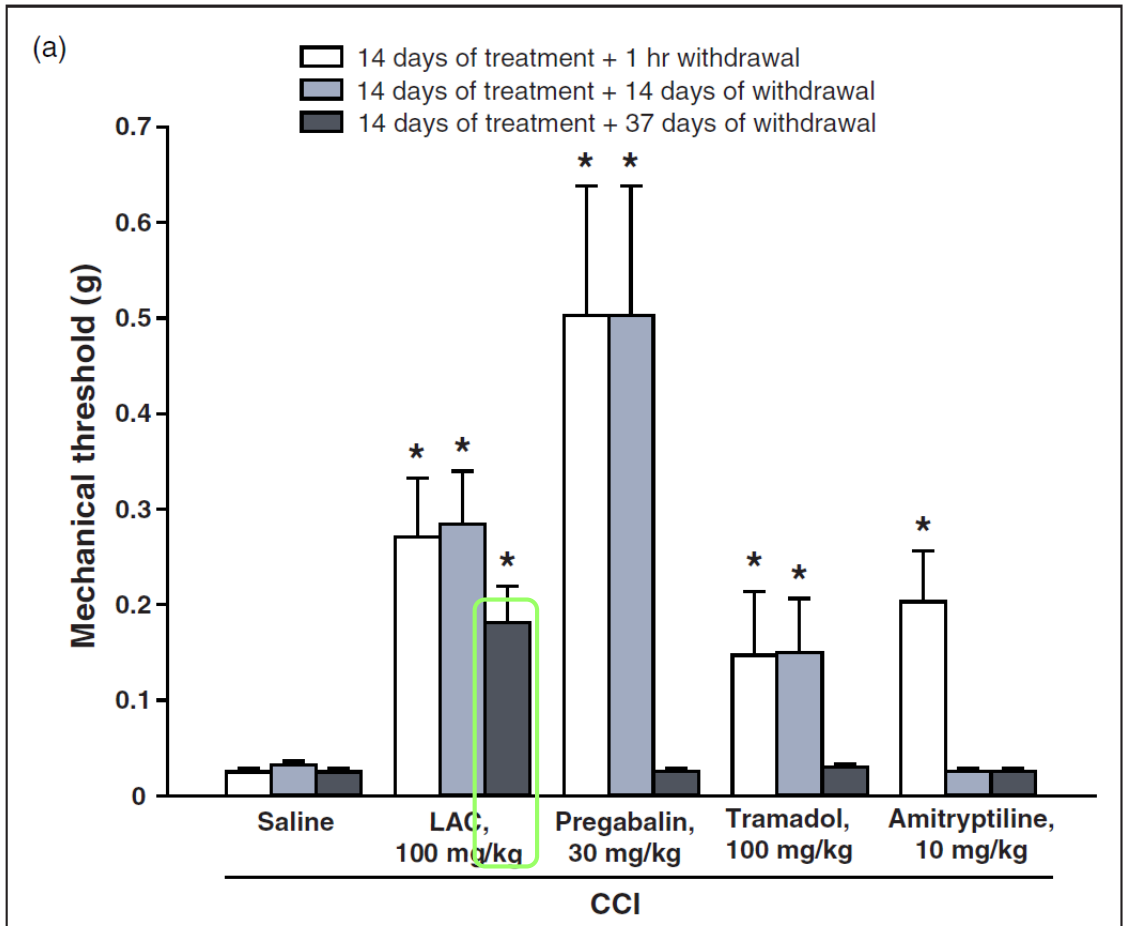


Studio su modello di Dolore Neuropatico da compressione cronica (CCI).

Dopo 37 gg dal termine del trattamento nel gruppo trattato con ALC si osserva ancora una sovra-espressione di mGLU2.

Mol Pain. 2017 Jan;13:1744806917697009

L'Azione analgesica di LAC perdura oltre il termine del trattamento

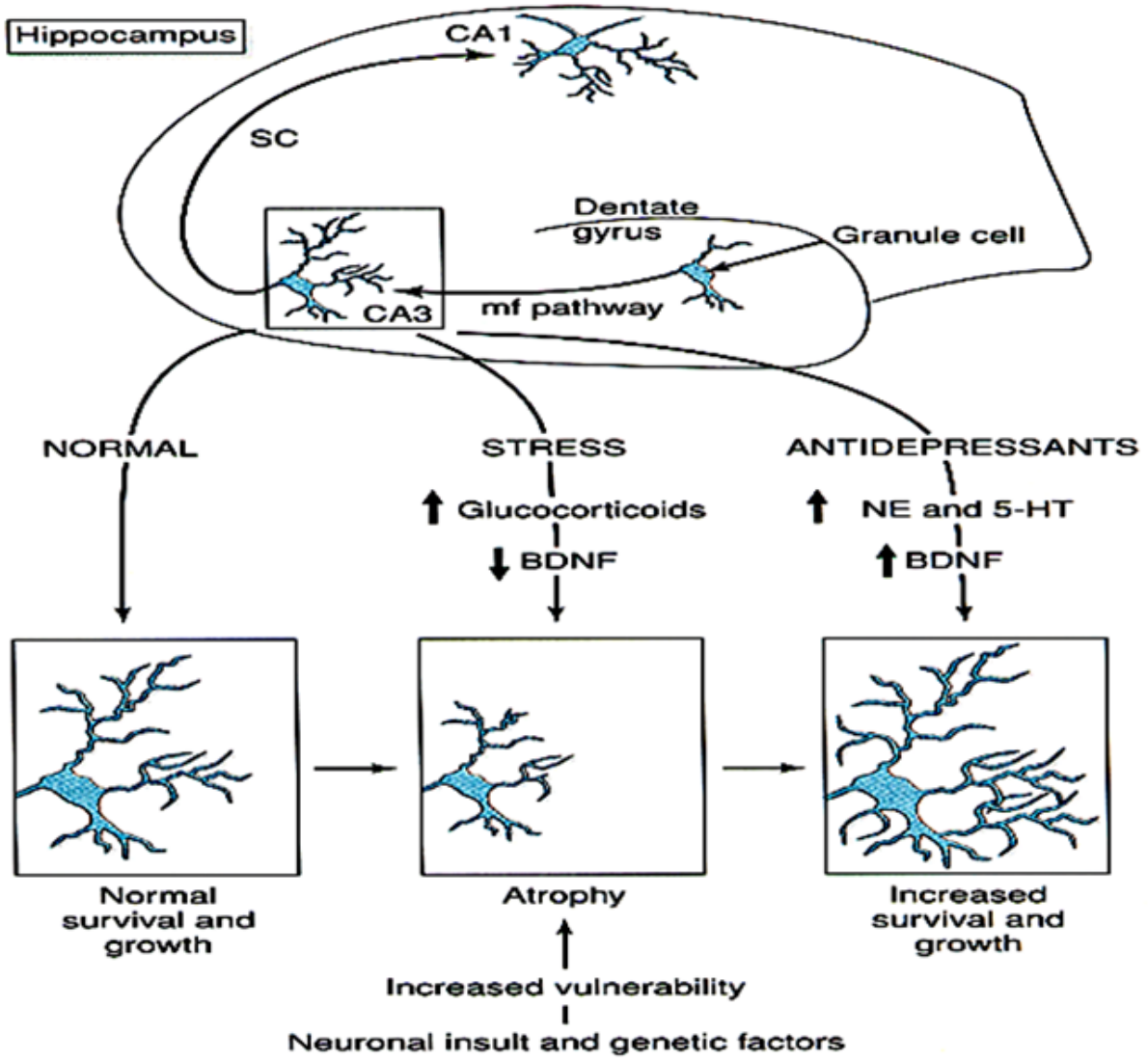


Soglia del dolore in modello di Dolore Neuropatico da compressione cronica (CCI).

Dopo 37 gg dal termine del trattamento solo ALC ha ancora effetto antiallodinico.

Notartomaso, Molecular Pain 2017

Azione antidepressiva di LAC


Hippocampus
CA1
SC
Dentate gyrus
Granule cell
CA3
mf pathway
NORMAL
STRESS
ANTIDEPRESSANTS
Glucocorticoids
BDNF
NE and 5-HT
BDNF
Normal survival and growth
Atrophy
Increased survival and growth
Increased vulnerability
Neuronal insult and genetic factors

PRINCIPAL FIBROMYALGIA SYMPTOMS

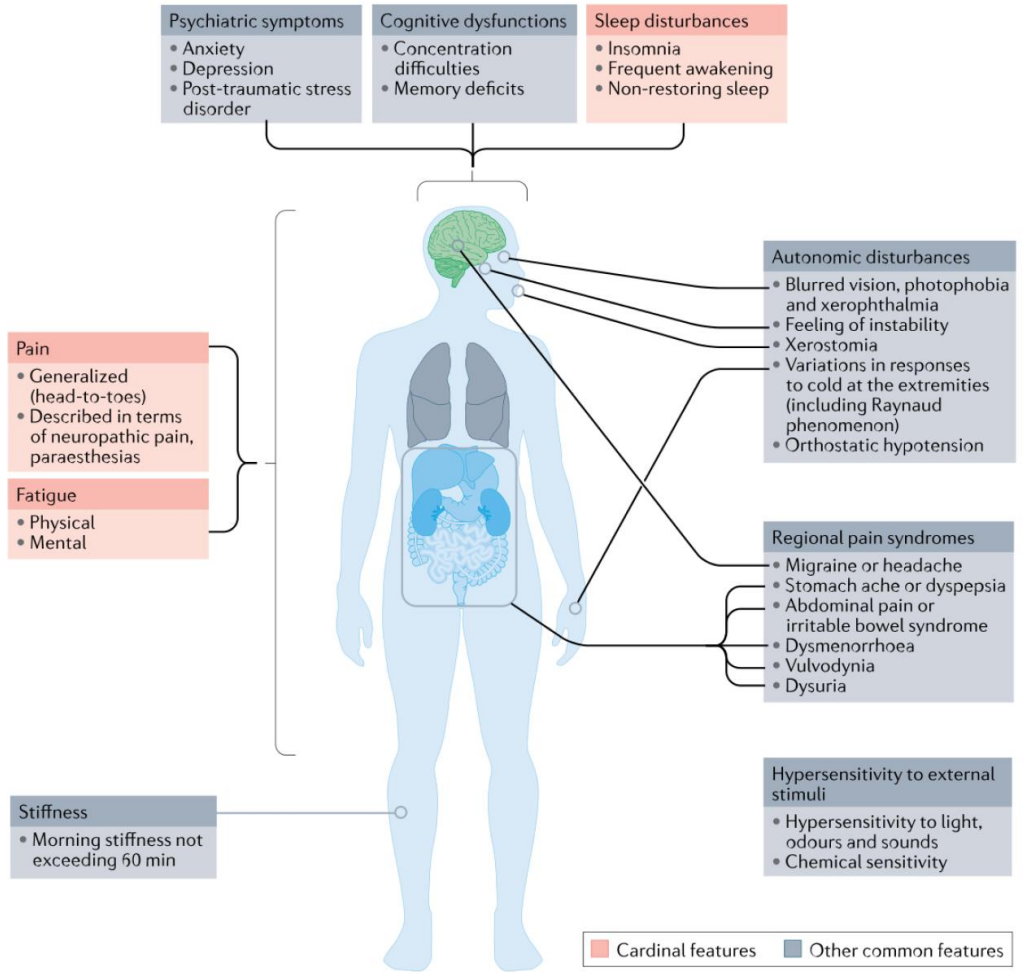
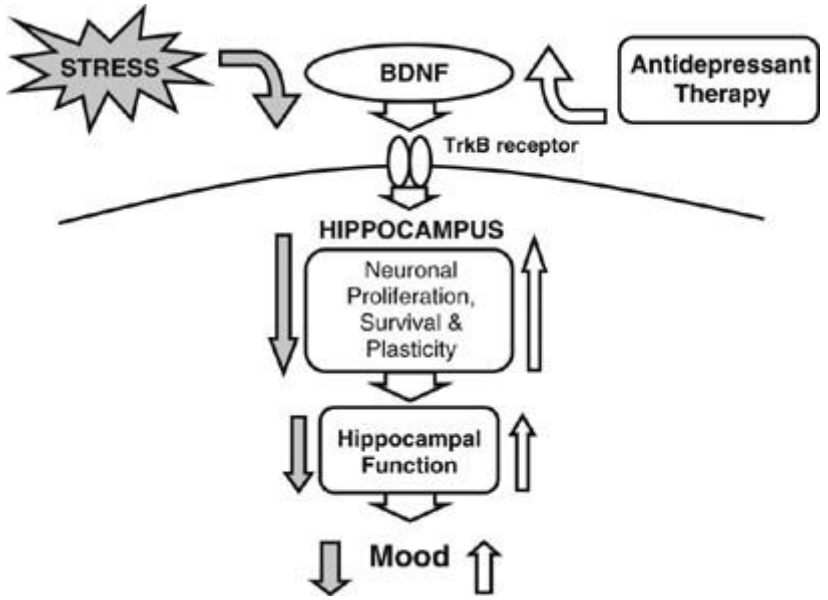


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be are divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other common features (shown in in grey).

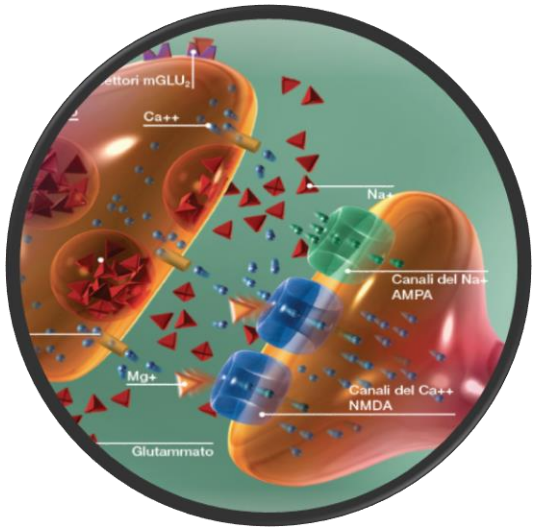
Sarzi-Puttini P *et al.* *Nature Rev Rheumatol* 2020 16: 645-660


STRESS
BDNF
Antidepressant Therapy
TrkB receptor
HIPPOCAMPUS
Neuronal Proliferation, Survival & Plasticity
Hippocampal Function
Mood

L’upregulation degli m-GLU2 potrebbe essere coinvolta negli effetti antidepressivi di LAC

Neuropsychopharmacology (2013) 38, 2220–2230

www.neuropsychopharmacology.org



Upregulation of mGlu2 Receptors via NF-κB p65 Acetylation Is Involved in the Proneurogenic and Antidepressant Effects of Acetyl-L-Carnitine

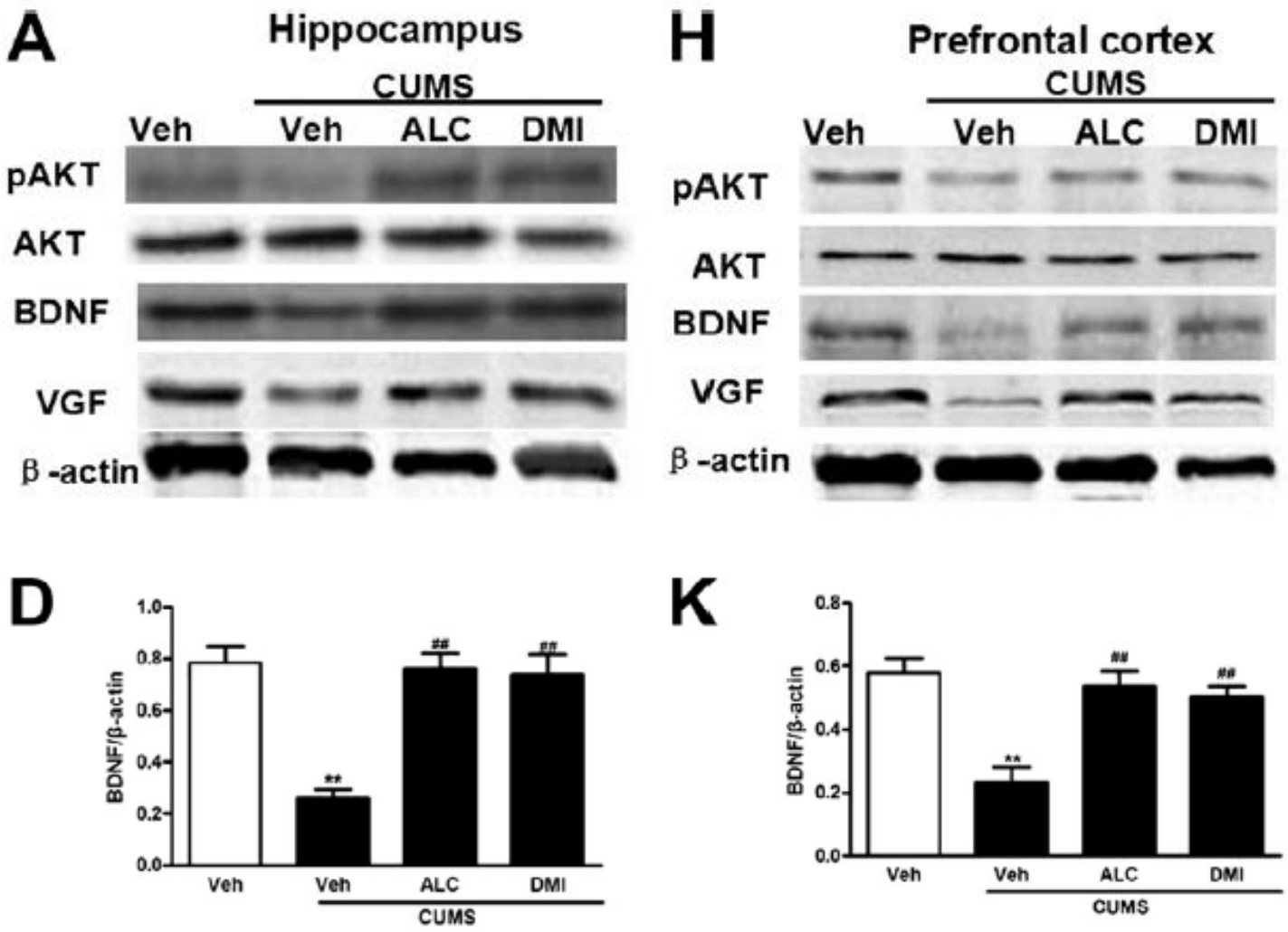
Bruna Cuccurazzu[1,2,4], Valeria Bortolotto[1,2,4], Maria Maddalena Valente[1,2], Federica Ubezio[1,2], Aleardo Koverech[3], Pier Luigi Canonico[2] and Mariagrazia Grilli*[,1,2]

[1]Laboratory of Neuroplasticity and Pain, University of Piemonte Orientale “A. Avogadro”, Novara, Italy; [2]Department of Pharmaceutical Sciences, University of Piemonte Orientale “A. Avogadro”, Novara, Italy; [3]University of Rome Sapienza, Rome, Italy

Table 1. Schedule of stressors used in the 21 days of CUMS procedure

Stressor	Duration	Day
Food deprivation	24-h	Monday
Exposure to a foreign object	24-h	
Water deprivation	24-h	
Forced swimming at 12 °C	6-min	Tuesday
Soiled cage	24-h	
Overnight illumination	Overnight	
Food deprivation	24-h	Wednesday
Cage tilt (45 °C)	7-h	
Physical restraint	2-h	
Exposure to an empty bottle	1-h	Thursday
Cage tilt (45 °C)	7-h	
Overnight illumination	Overnight	
Soiled cage	24-h	Friday
Forced swimming at 12 °C	6-min	
Physical restraint	2-h	
Exposure to a foreign object	24-h	Saturday
Forced swimming at 12 °C	6-min	
Cage tilt (45 °C)	7-h	
Soiled cage	24-h	Sunday
Exposure to an empty bottle	1-h	
Overnight illumination	Overnight	

EFFETTI DELLA LAC SULL'ESPRESSIONE DEL BDNF



Neuroscience 285 (2015) 281–291

L-acetil-carnitina in pazienti con dolore cronico:

effetti su depressione e tono dell'umore

International Journal of *Molecular Sciences*

MDPI

Review

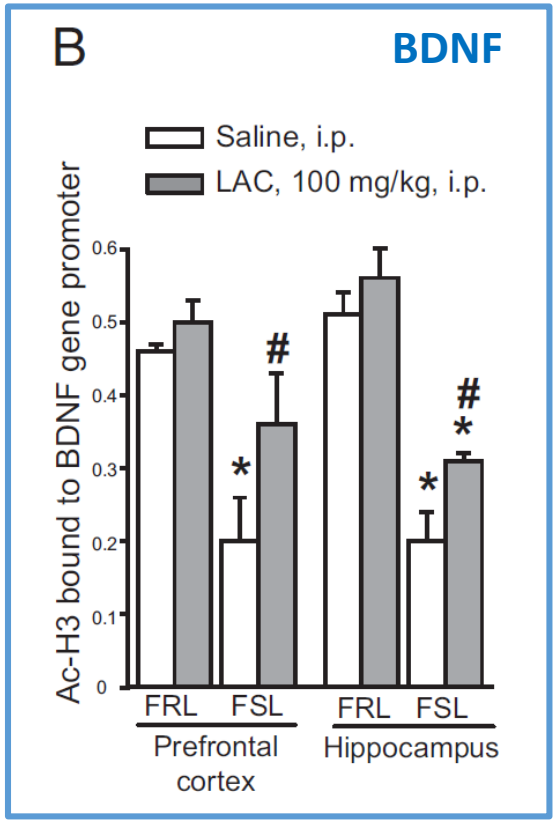
L-Acetylcarnitine: A Mechanistically Distinctive and Potentially Rapid-Acting Antidepressant Drug

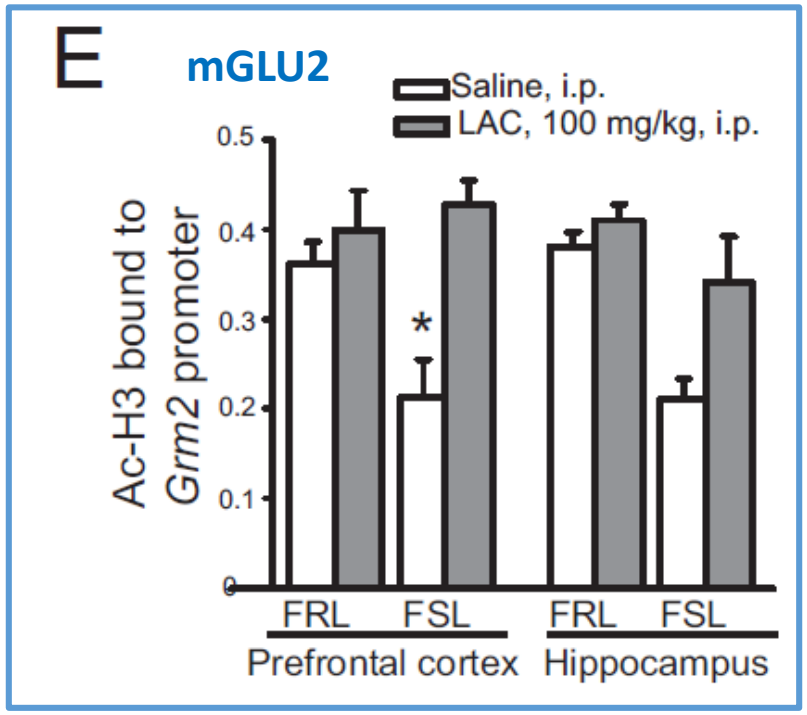
Santina Chiechio [1], Pier Luigi Canonico [2] and Mariagrazia Grilli [3,*]

1 Department of Drug Sciences, Section of Pharmacology and Toxicology, University of Catania, 95125 Catania, Italy; chiechio@unict.it
2 Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy; pierluigi.canonico@uniupo.it
3 Laboratory of Neuroplasticity, Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy

EFFETTO EPIGENETICO

LAC aumenta i livelli di **acetilazione degli istoni** in corrispondenza delle sequenze promoter per i geni che codificano per **BDNF e mGLU2** nella corteccia prefrontale e nell'ippocampo.

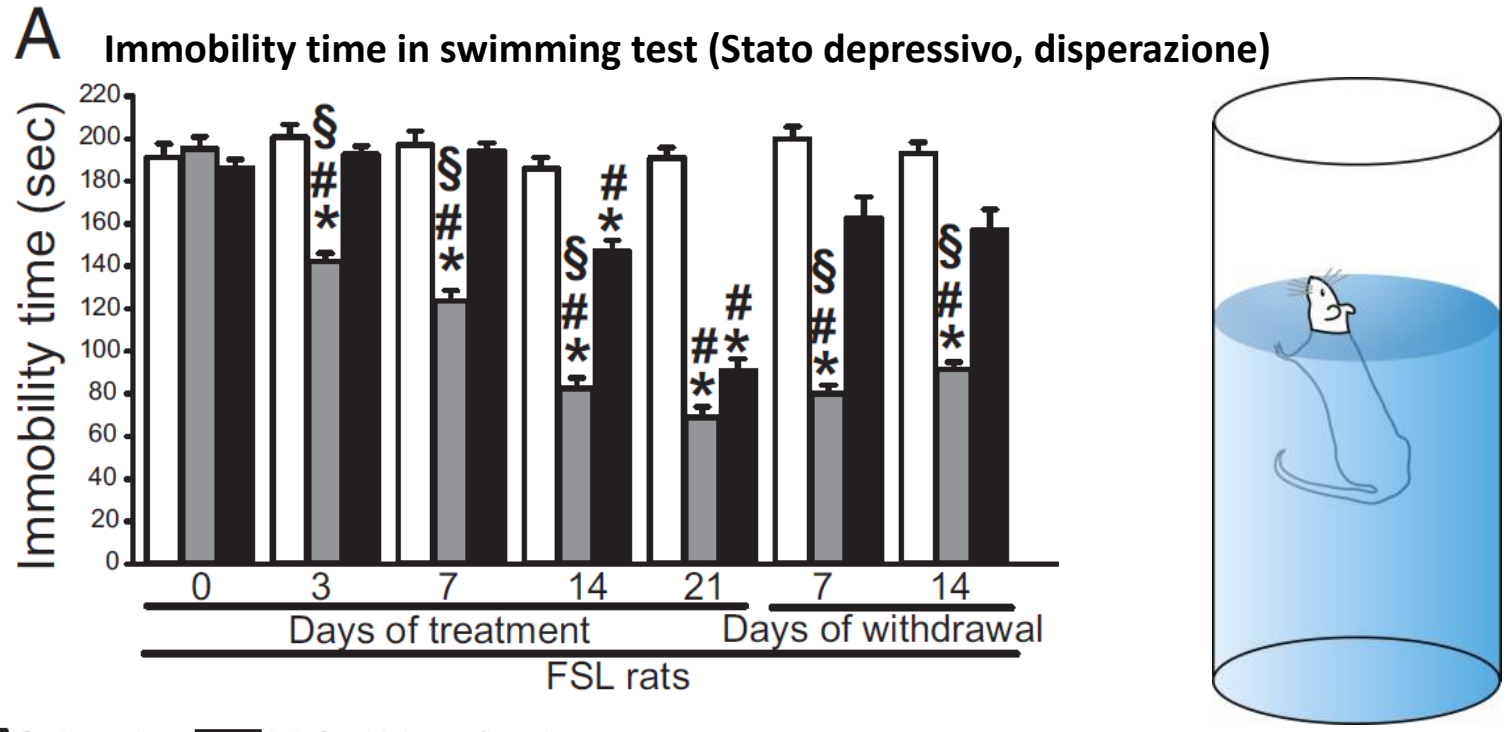




Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

LAC migliora rapidamente lo stato depressivo in modello animale di depressione

- LAC migliora lo stato depressivo già **dopo 3 giorni** di trattamento, clomipramina dopo 14 giorni.
- LAC mantiene l'effetto **fino a 14 gg dopo il termine del trattamento**, mentre clomipramina lo perde appena il trattamento viene interrotto

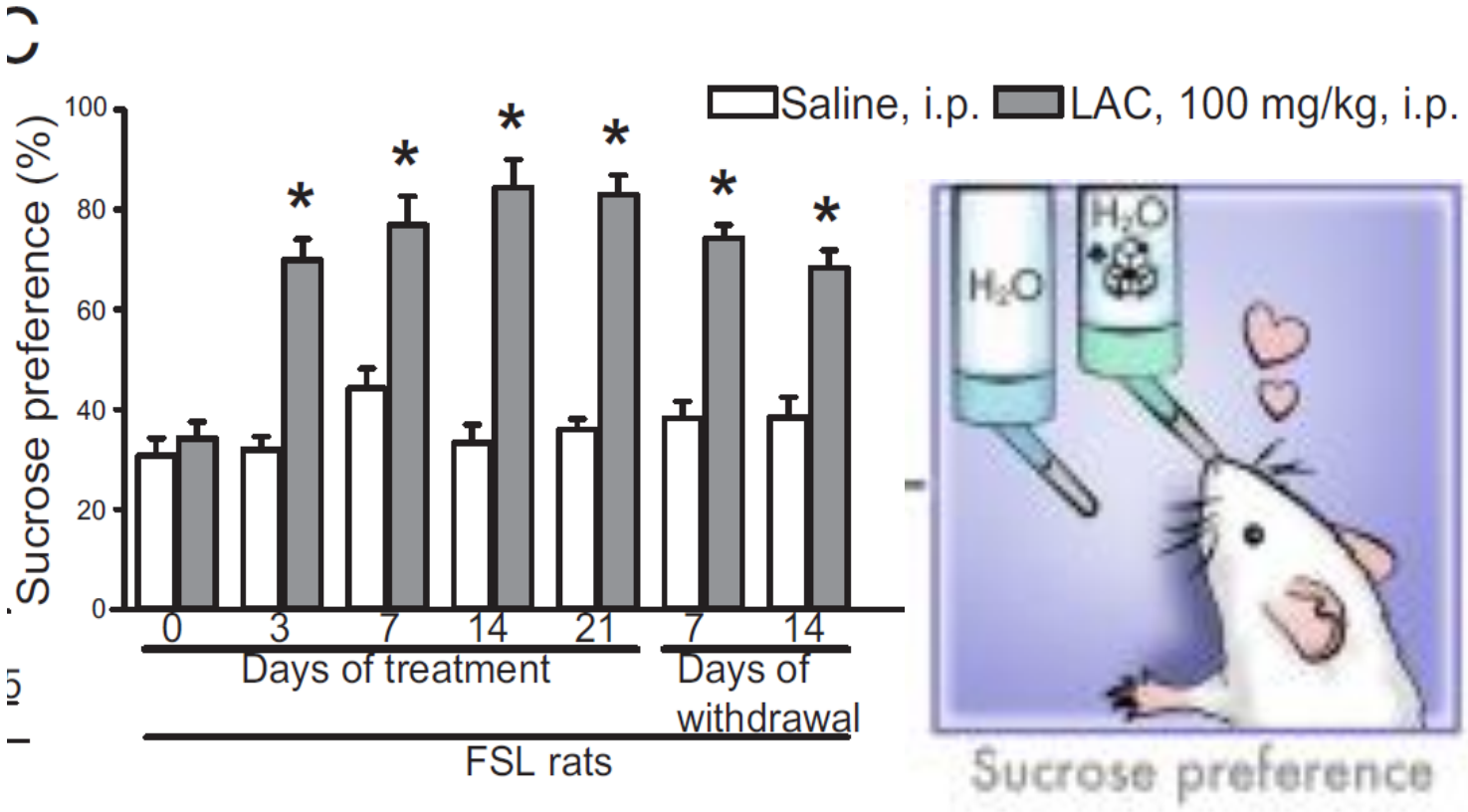


Clomipramina: antidepressivo triciclico (es. Anafranil)

Nasca C et al. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

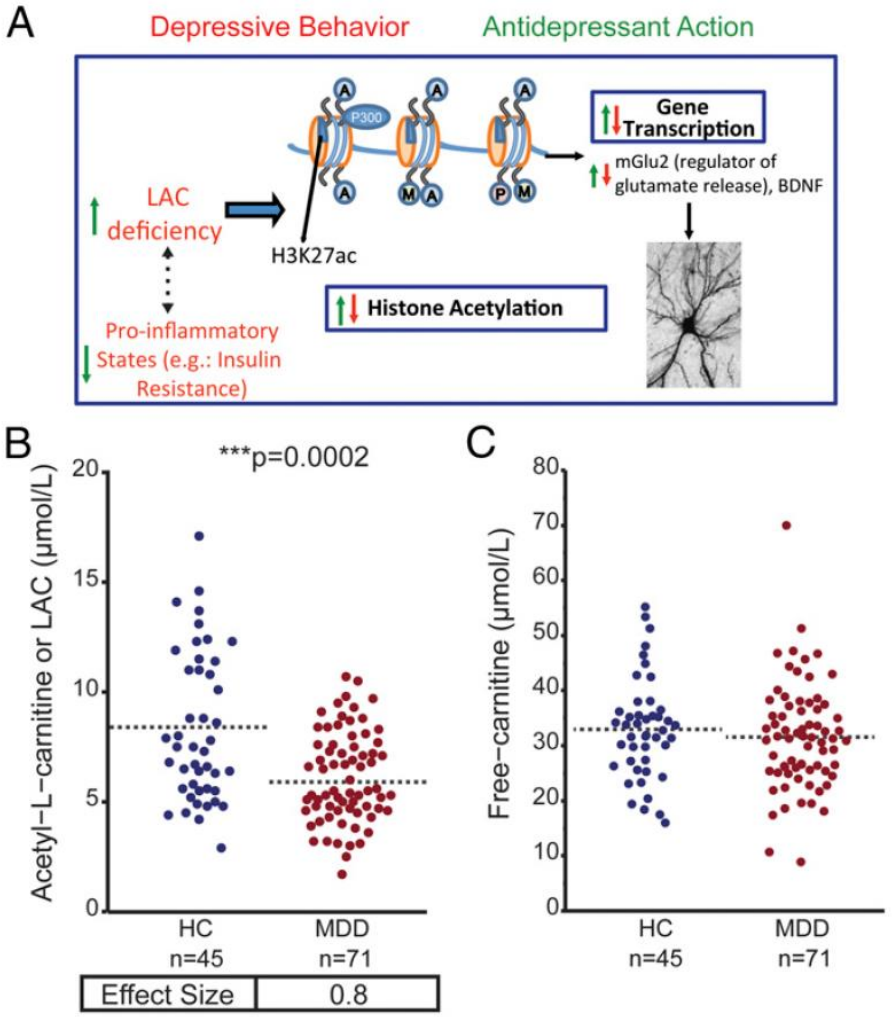
LAC migliora rapidamente e in modo marcato e prolungato lo stato di anedonia

Sucrose preference test (anedonia)



Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

L-Acetil-Carnitina risulta carente nel plasma di pazienti con depressione maggiore



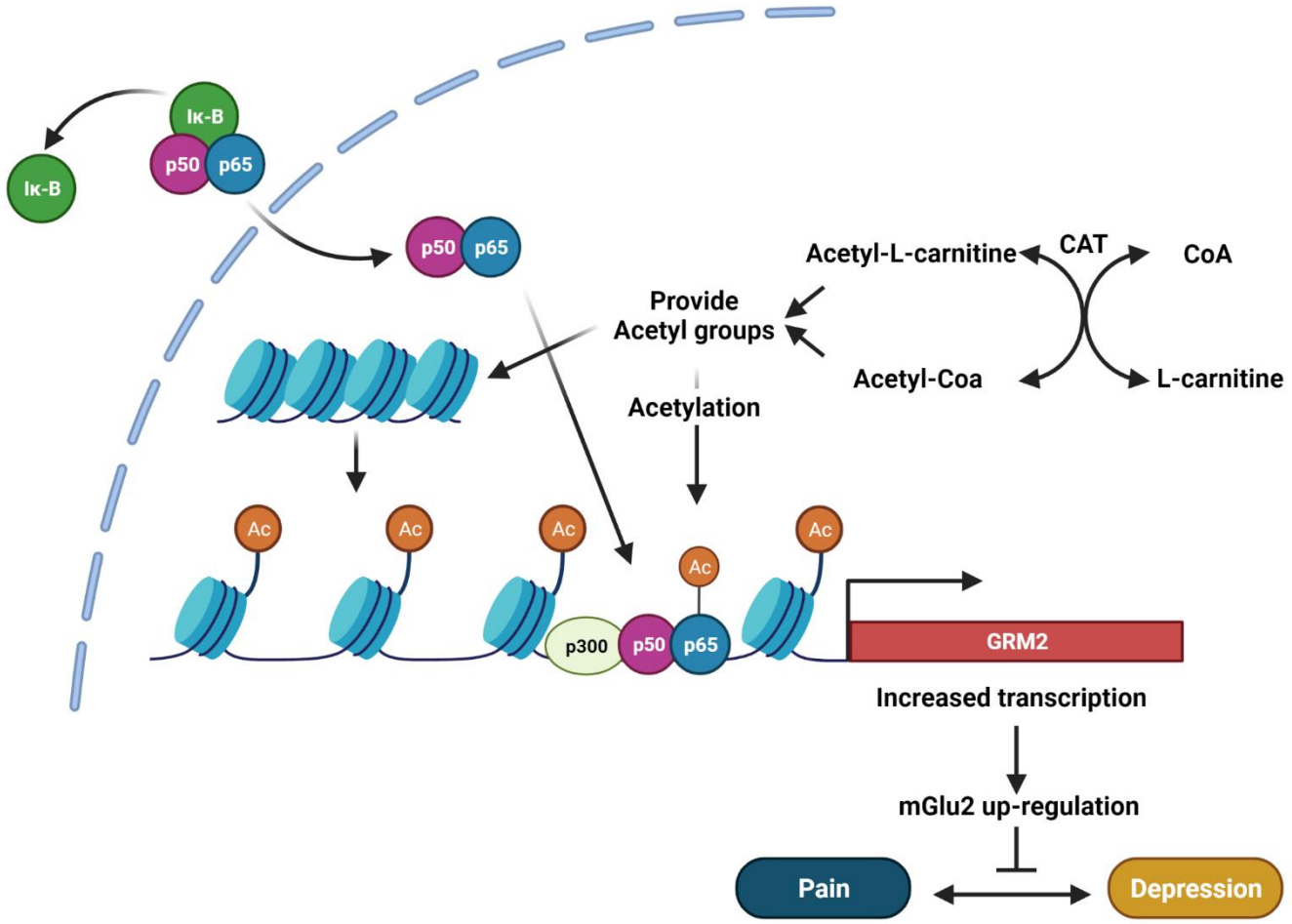
Nasca C et al. Acetyl-L-carnitine deficiency in patients with major depressive disorder. PNAS 2018;115(34):8627-8632

Table 1. Summary of randomized, placebo or comparator controlled, clinical trials of acetyl-L-carnitine in treatment of depression.

Author (year)	Primary diagnosis	Length (weeks)	Type and dosage of ALC	Type and dosage of comparator	Efficacy results	Ref.
Bersani *et al.* (2013)	Dysthymic disorder (elderly)	7	ALC (3 g); n = 41	FOX (20 mg); n = 39	ALC = FOX in HDS-21, HAM-A, and BDI	[32]
Brennan *et al.* (2013)	Bipolar depression	12	ALC (1–3 g) + ALA (0.61.8 g); n = 20	PBO; n = 20	ALC + ALA = PBO in MADRS, HDS-21, YMRS, and CGI	[28]
Zanardi & Smeraldi (2006)	Dysthymic disorder	12	ALC (1 g); n = 99	ASP (100 mg); n = 94	ALC comparable to ASP in HDS-21, MADRS, CDRS, and CGI	[31]
Villardita *et al.* (1993)	MDD	6	ALC (1.5 g); n = 14	PBO	ALC > PBO in HDS***	[24]
Gecele *et al.* (1991)	MDD (elderly)	6	ALC (2 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17*	[27]
Fulgente *et al.* (1990)	Dysthymic disorder	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17***	[30]
Garzya *et al.* (1990)	MDD (elderly)	8	ALC (1.5 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17**	[26]
Bella *et al.* (1990)	Dysthymic disorder (elderly)	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17****	[29]
Nasca *et al.* (1989)	Depression	8	MIA + ALC (2 g); n = 10 MIA + PBO	MIA + PBO; n = 10	MIA + ALC > MIA + PBO in HDS***	[25]

*p < 0.05.
**p < 0.01.
***p < 0.001 versus comparator.
ALC: Acetyl-L-carnitine; ASP: Amisulpride; BDI: Beck depression inventory; CDRS: Cornell dysthymia rating scale; CGI: Clinical global impression scale; FOX: Fluoxetine; HAM-A: Hamilton anxiety rating scale; HDMS: Hamilton depression and melancholia scale; HDS: Hamilton depression rating scale; MADRS: Montgomery-åsberg depression rating scale; MDD: Major depressive disorder; MIA: Mianserine.

Wang S et al. Expert Rev Neurother 15(9), 1015–1029 (2015)



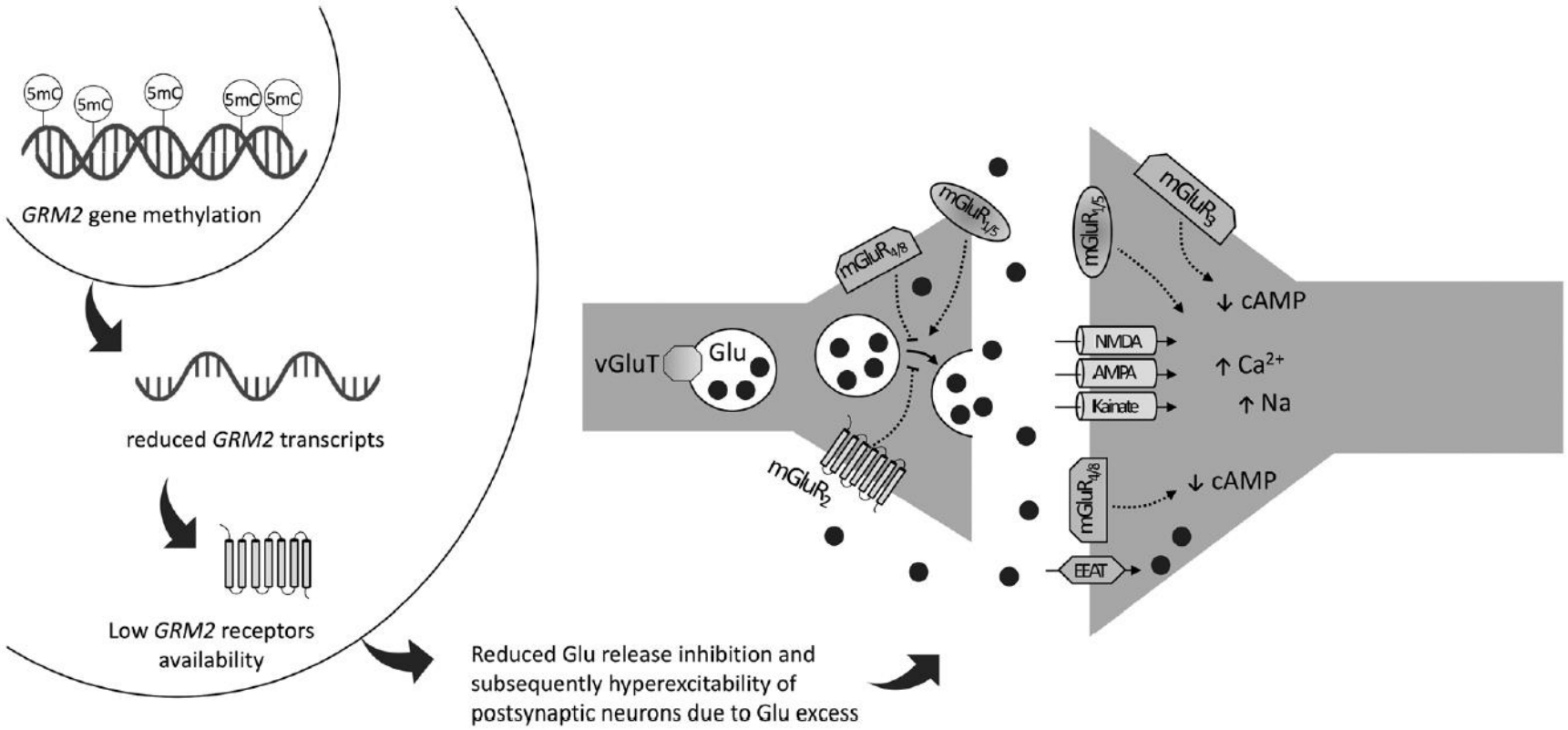
Pharmacol. Rev. 2021 *in press*

Original Experimental

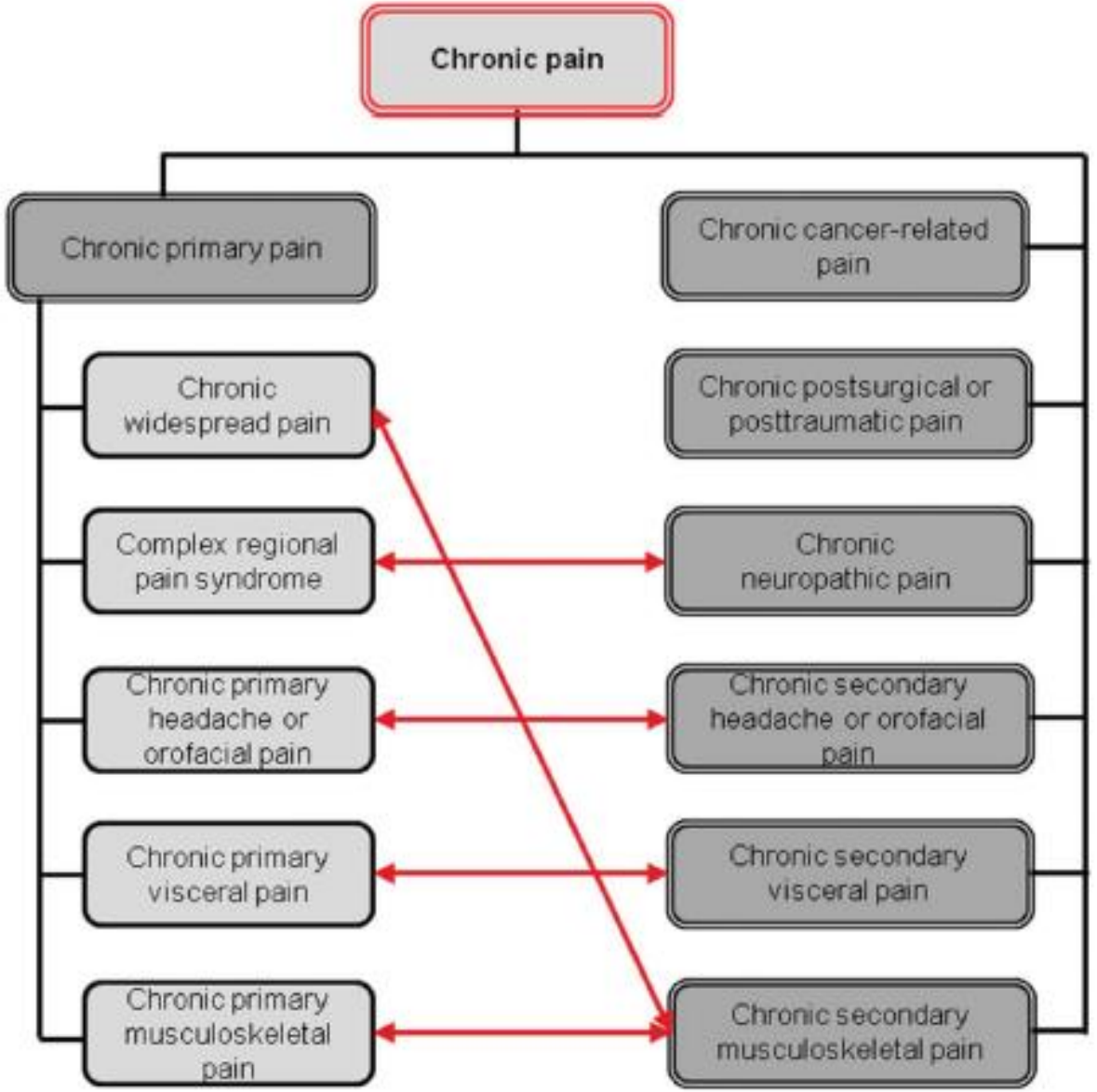
Maria Carla Gerra*, Davide Carnevali, Inge Søkilde Pedersen, Claudia Donnini, Matteo Manfredini, Alberto González-Villar, Yolanda Triñanes, Marina Pidal-Miranda, Lars Arendt-Nielsen and Maria Teresa Carrillo-de-la-Peña

DNA methylation changes in genes involved in inflammation and depression in fibromyalgia: a pilot study

Scand J Pain 2021; 21(2): 372–383



Scand J Pain 2021; 21(2): 372–383



Chronic secondary pain syndromes

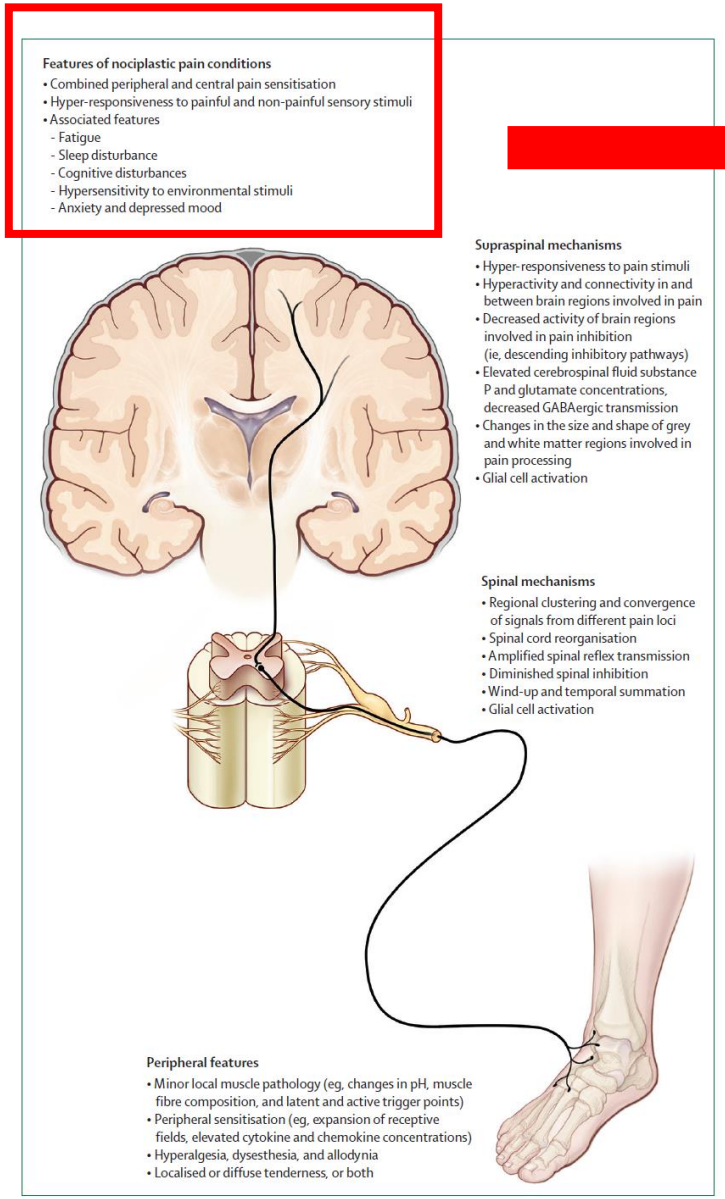
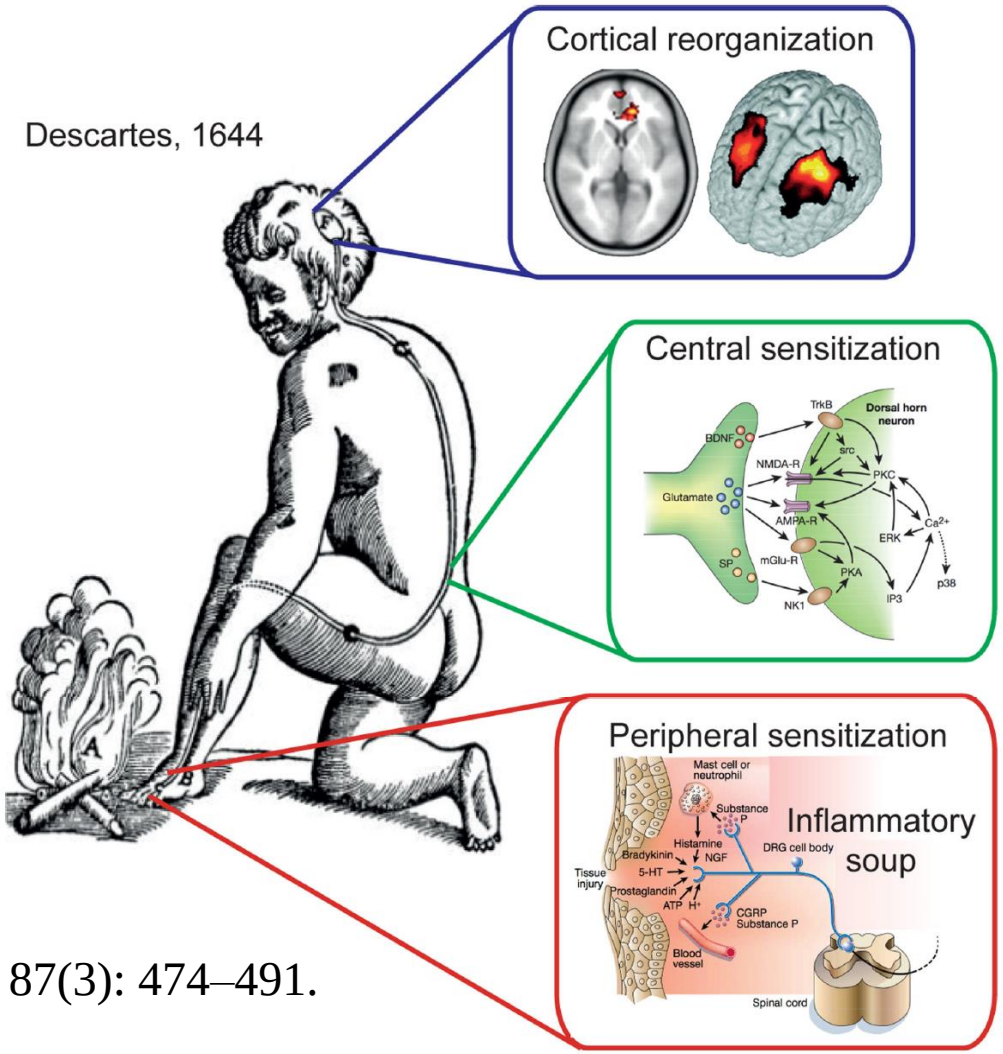


Figure: Mechanisms and features of nociplastic pain
Figure created by Joe Kanasz.

Features of nociplastic pain conditions

- Combined peripheral and central pain sensitisation
- Hyper-responsiveness to painful and non-painful sensory stimuli
- Associated features
  - Fatigue
  - Sleep disturbance
  - Cognitive disturbances
  - Hypersensitivity to environmental stimuli
  - Anxiety and depressed mood

Lancet 2021; 397: 2098–110



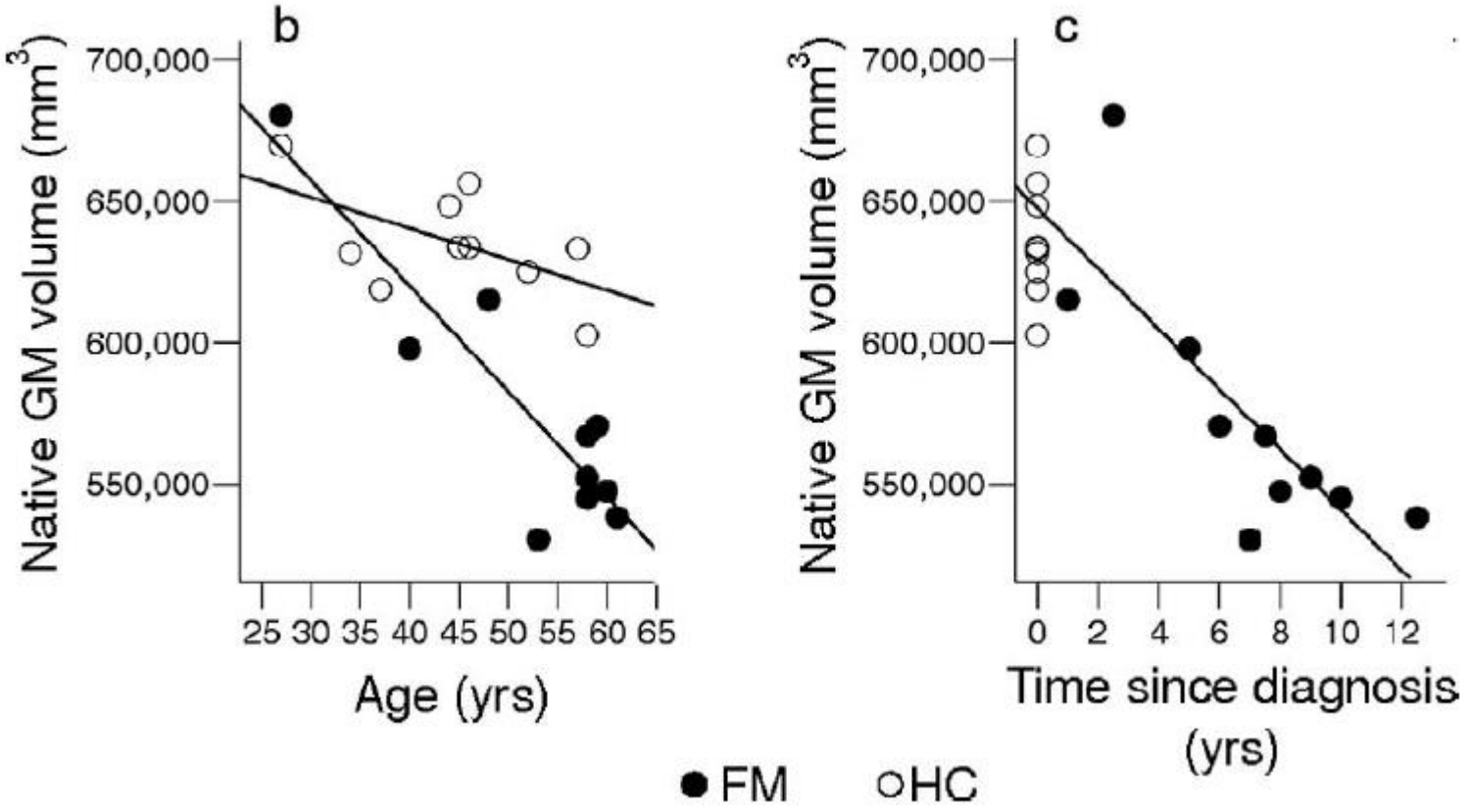
Neuron. 2015 August 5; 87(3): 474–491.

Brief Communications

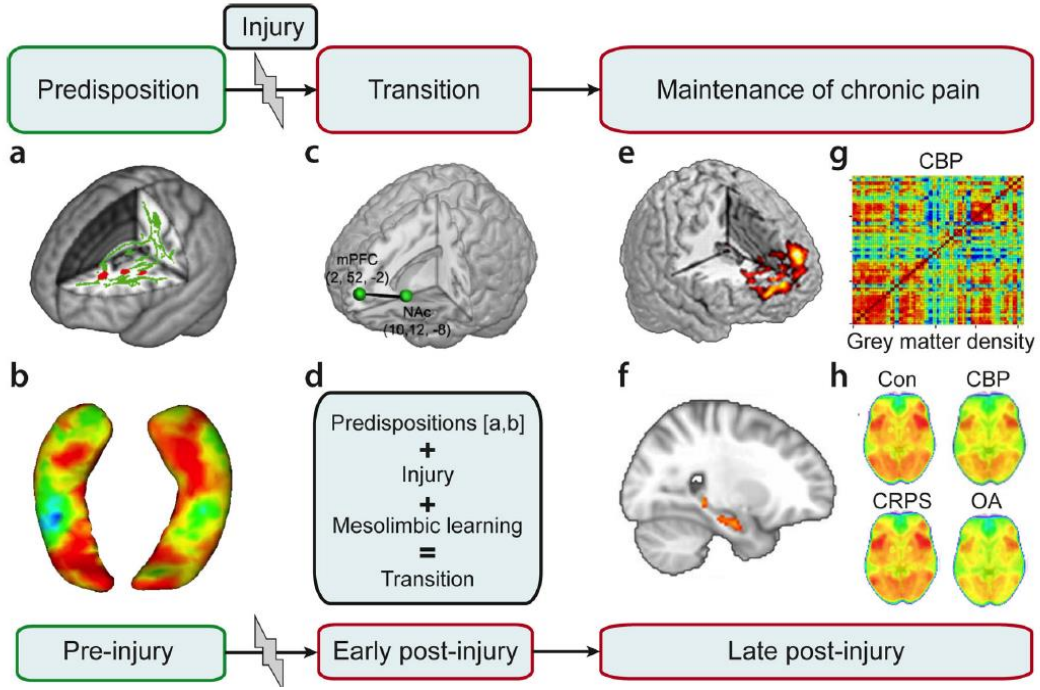
Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain?

Anil Kuchinad,[1,2] Petra Schweinhardt,[1] David A. Seminowicz,[1] Patrick B. Wood,[1] Boris A. Chizh,[4] and M. Catherine Bushnell[1,2,3]

[1]McGill Centre for Research on Pain, [2]Department of Neurology and Neurosurgery, and [3]Department of Anesthesia and Faculty of Dentistry, McGill University, Montreal, Quebec, Canada H3A 2B2, and [4]GlaxoSmithKline, Addenbrooke's Centre for Clinical Investigation, Addenbrooke's Hospital, Cambridge CB2 2GG, United Kingdom

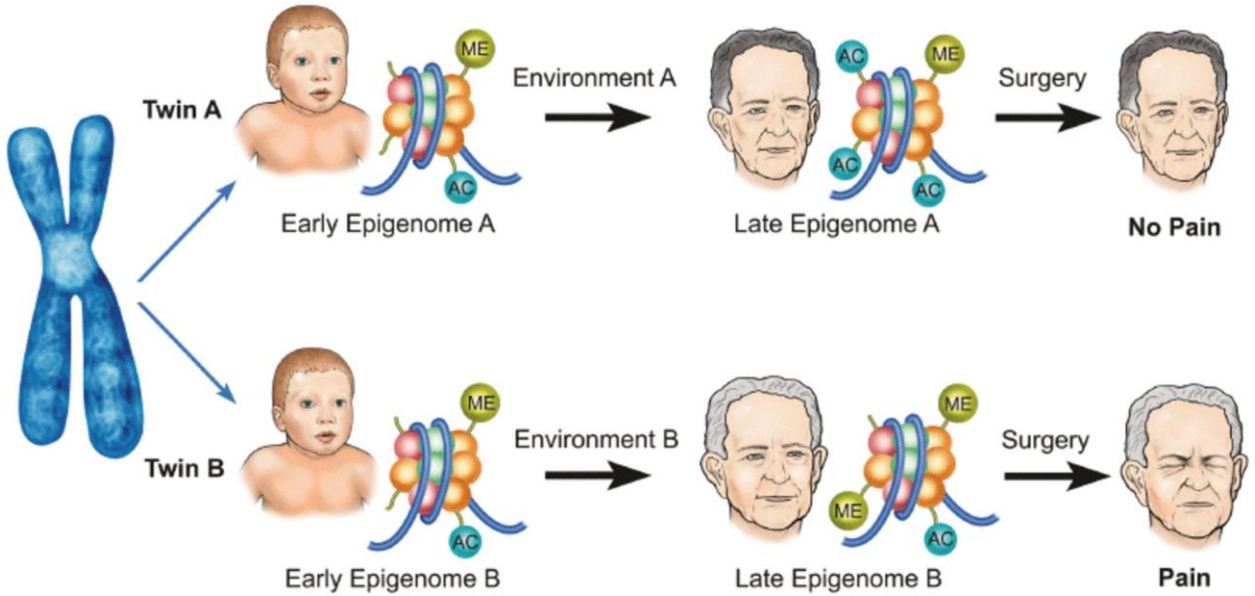


The Journal of Neuroscience, April 11, 2007 • 27(15):4004–4007



Neuron. 2015 August 5; 87(3): 474–491.

Figure 1 Epigenome and chronic pain. Twin A and Twin B demonstrate similar “epigenomes” at birth with few (if any) ...



Pain Medicine, Volume 13, Issue 11, November 2012, Pages 1474–1490, https://doi.org/10.1111/j.1526-4637.2012.01488.x

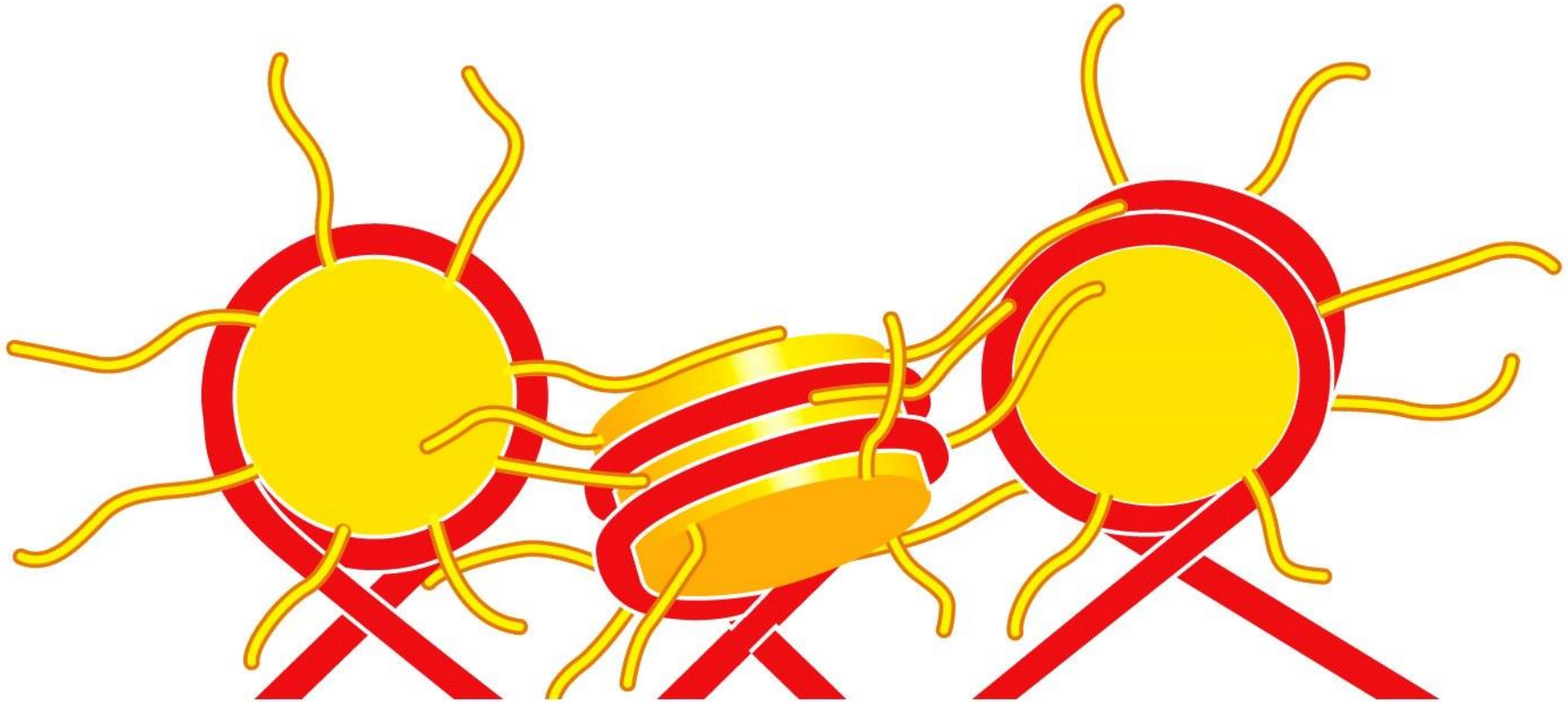


Figure 4-33b *Molecular Biology of the Cell* (© Garland Science 2008)

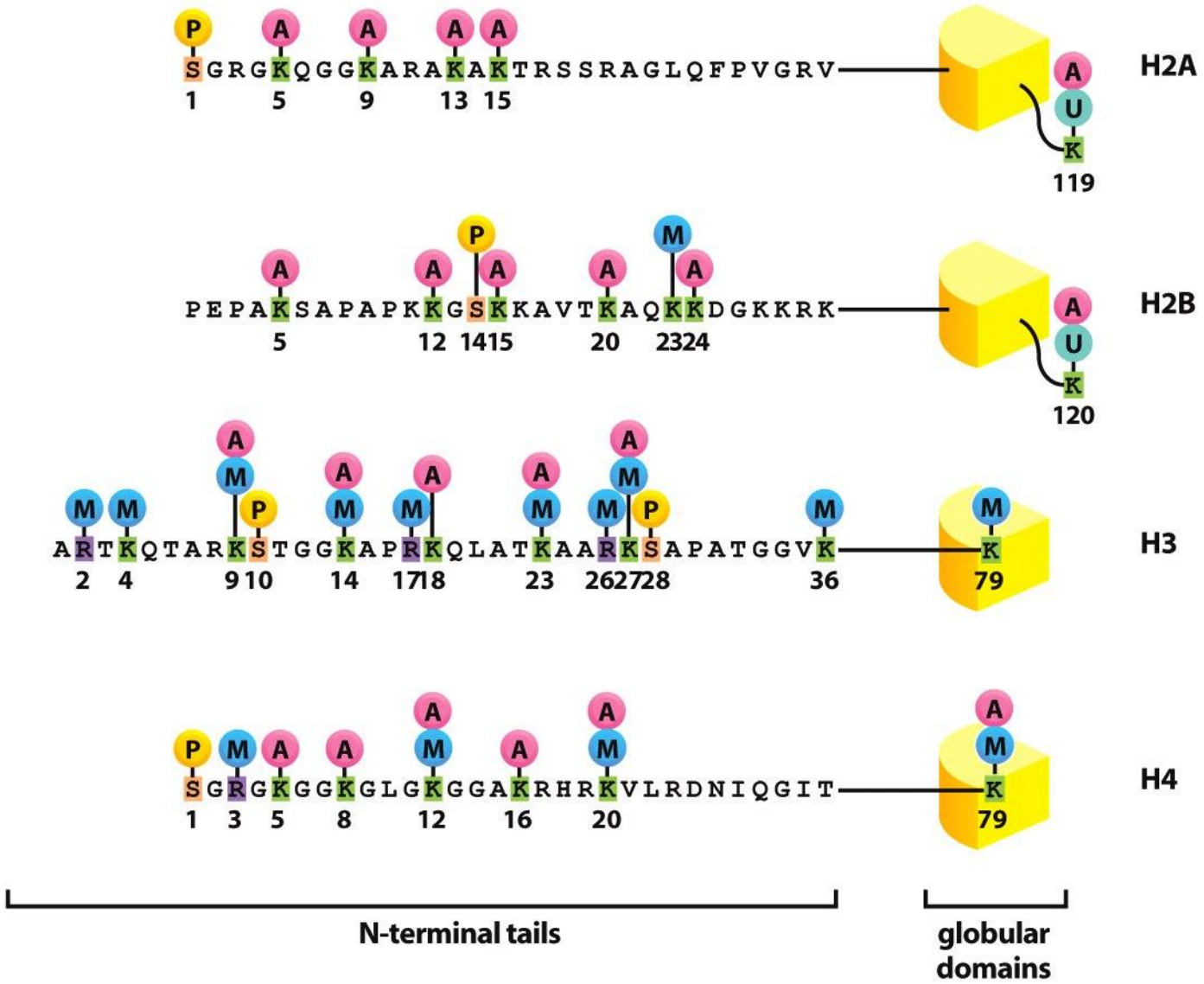
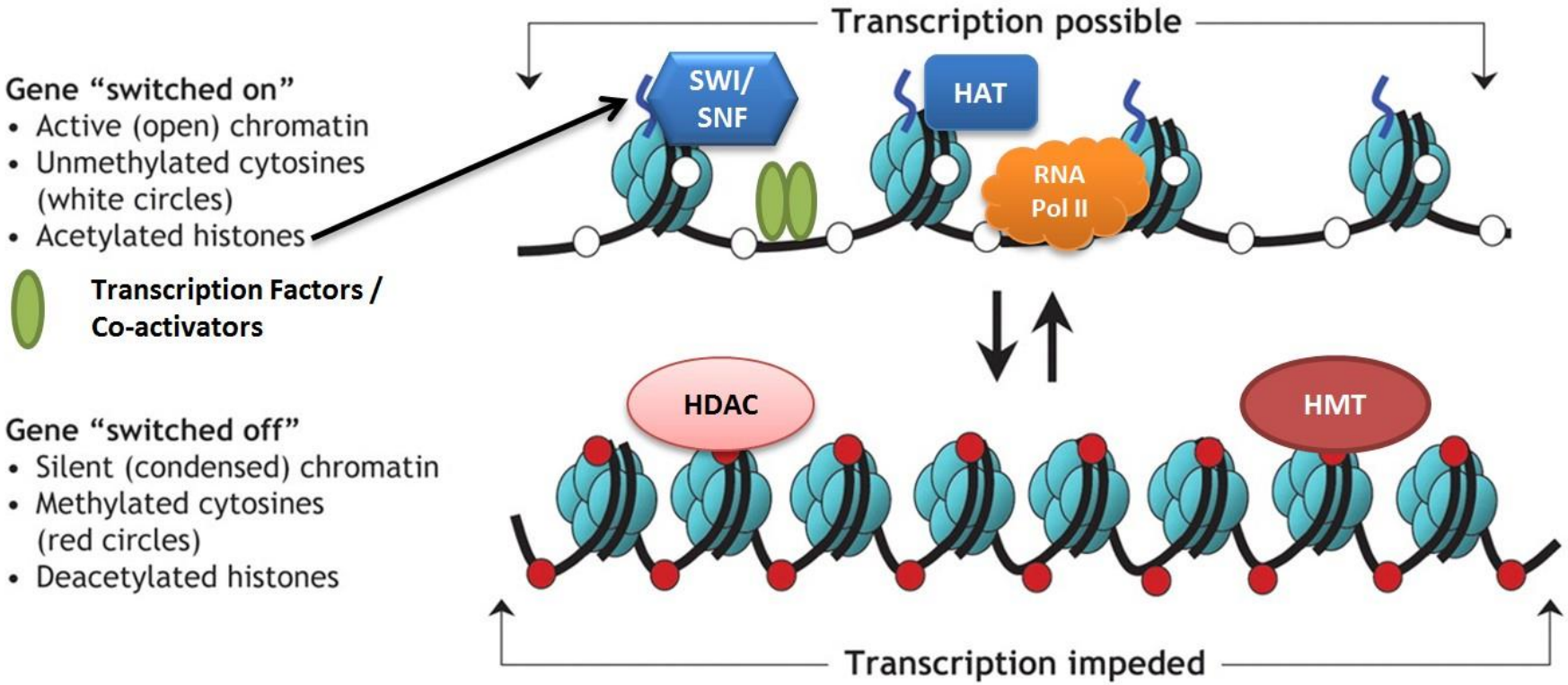
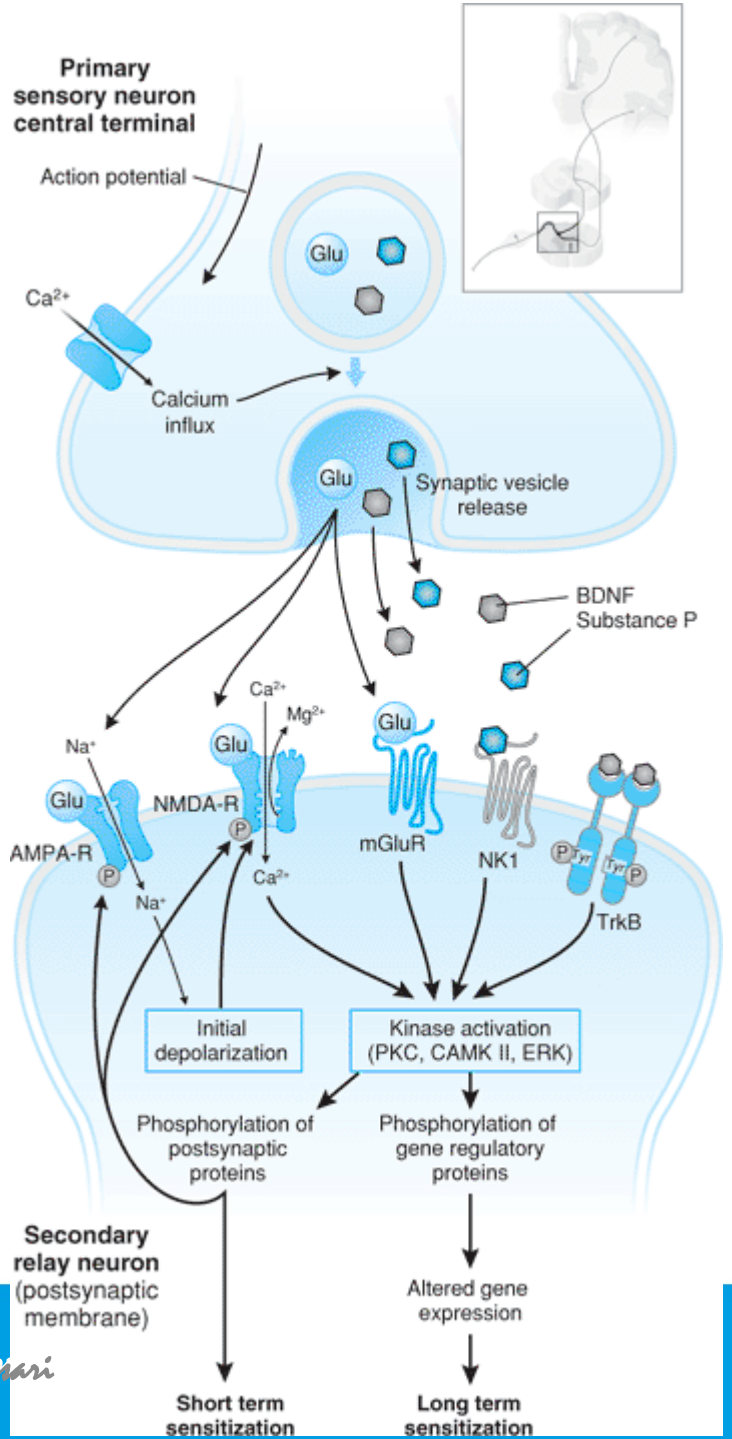
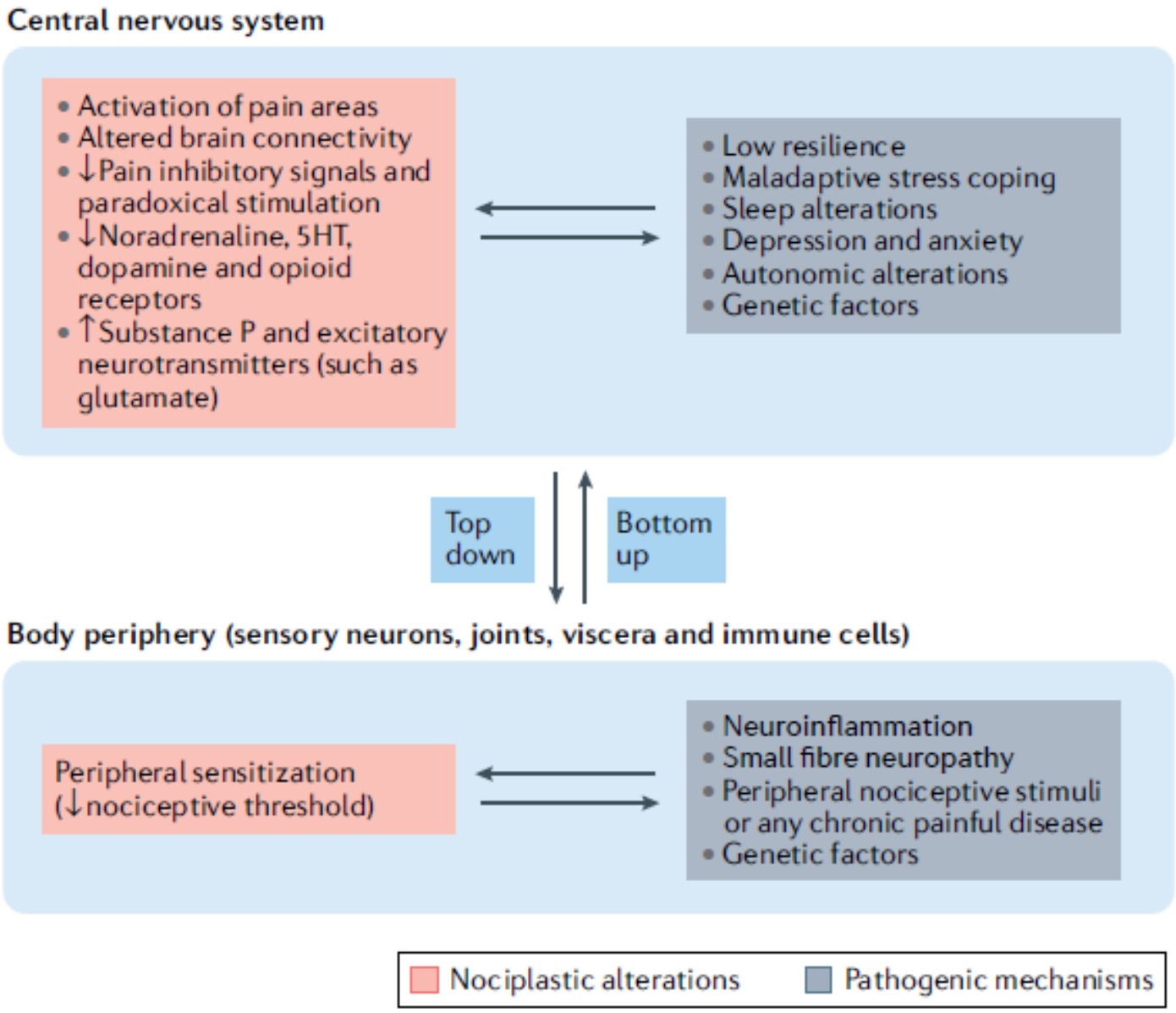


Figure 4-39b *Molecular Biology of the Cell* (© Garland Science 2008)

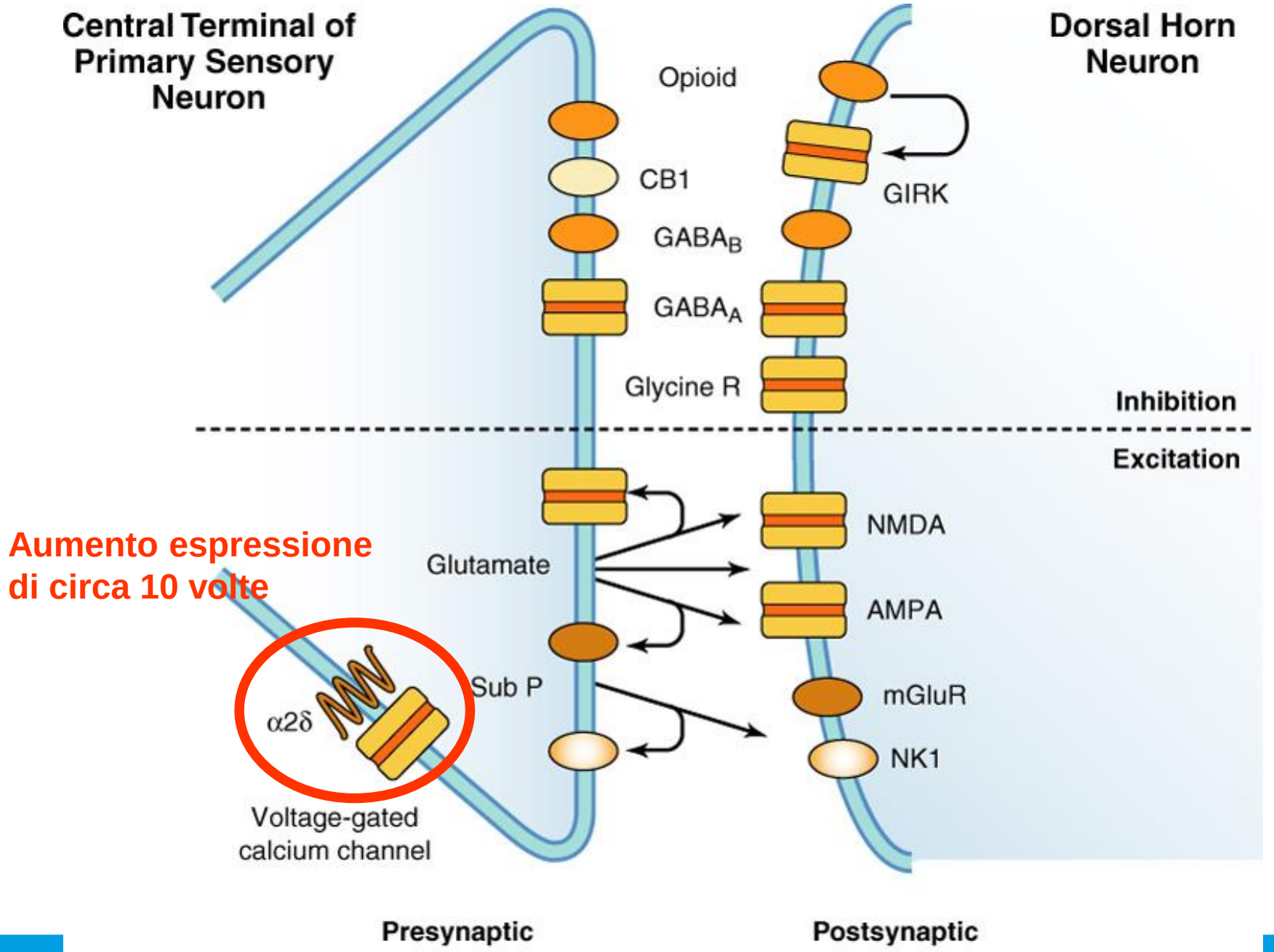

Transcription possible
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Transcription Factors / Co-activators
SWI/ SNF
HAT
RNA Pol II
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
HDAC
HMT
Transcription impeded

SENSIBILIZZAZIONE SPINALE

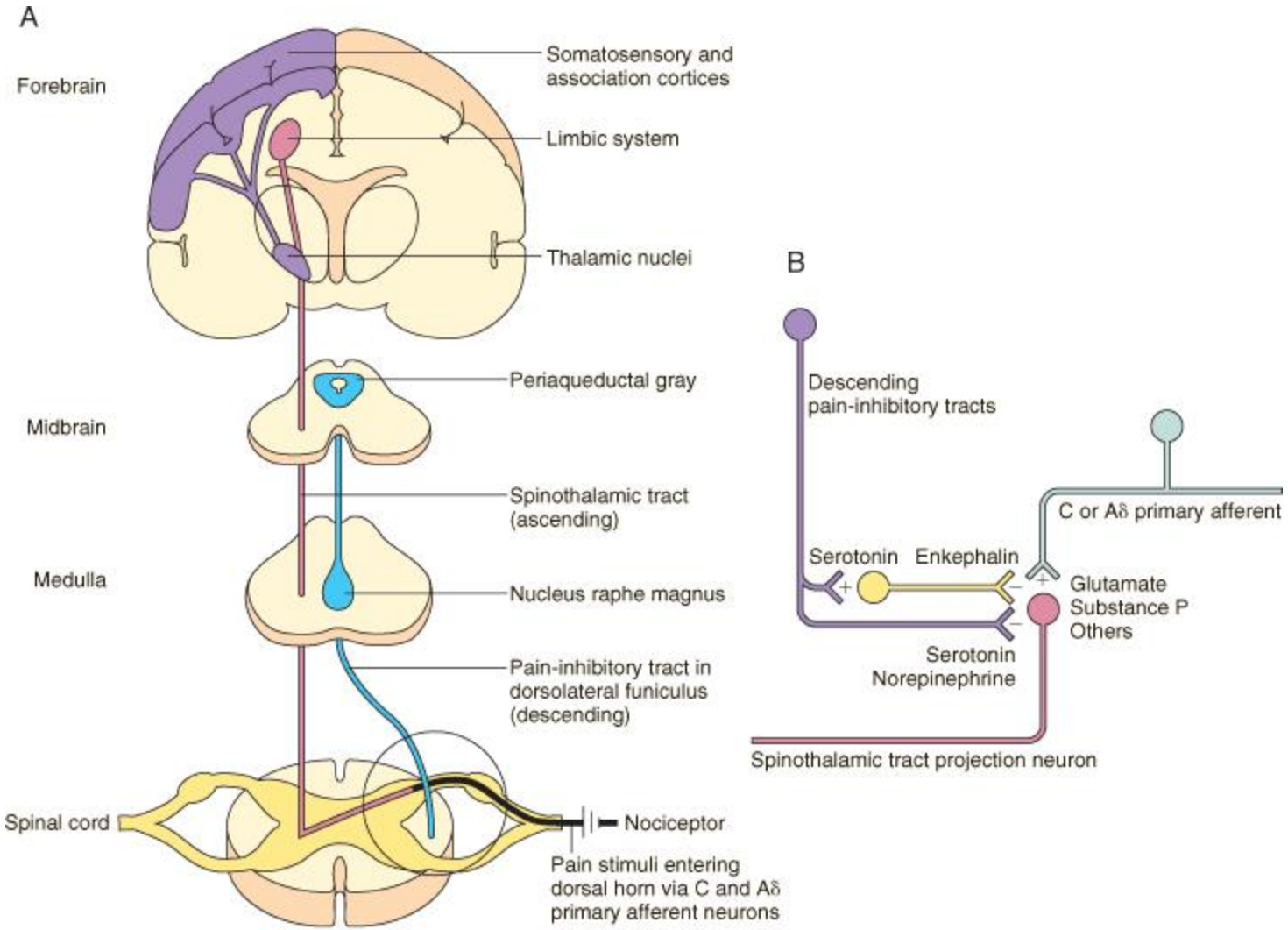


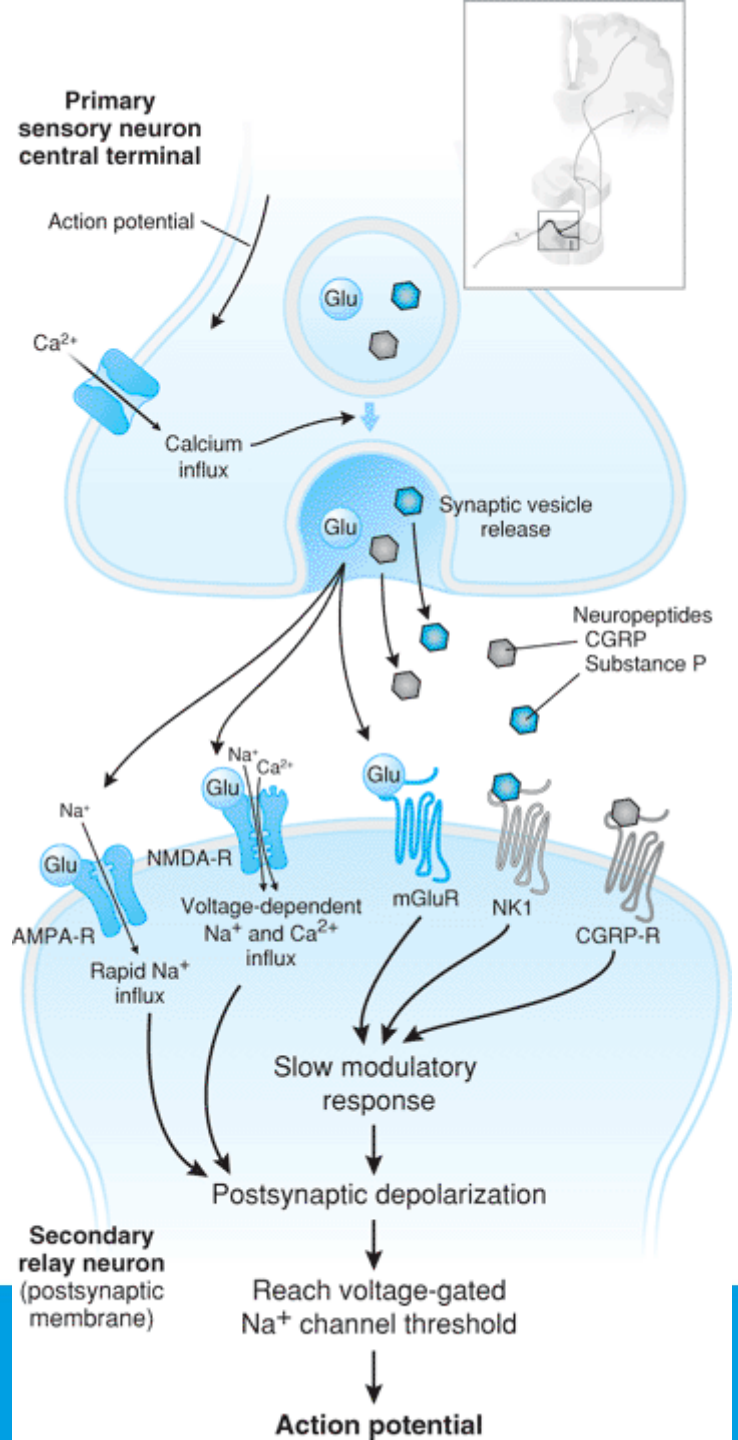


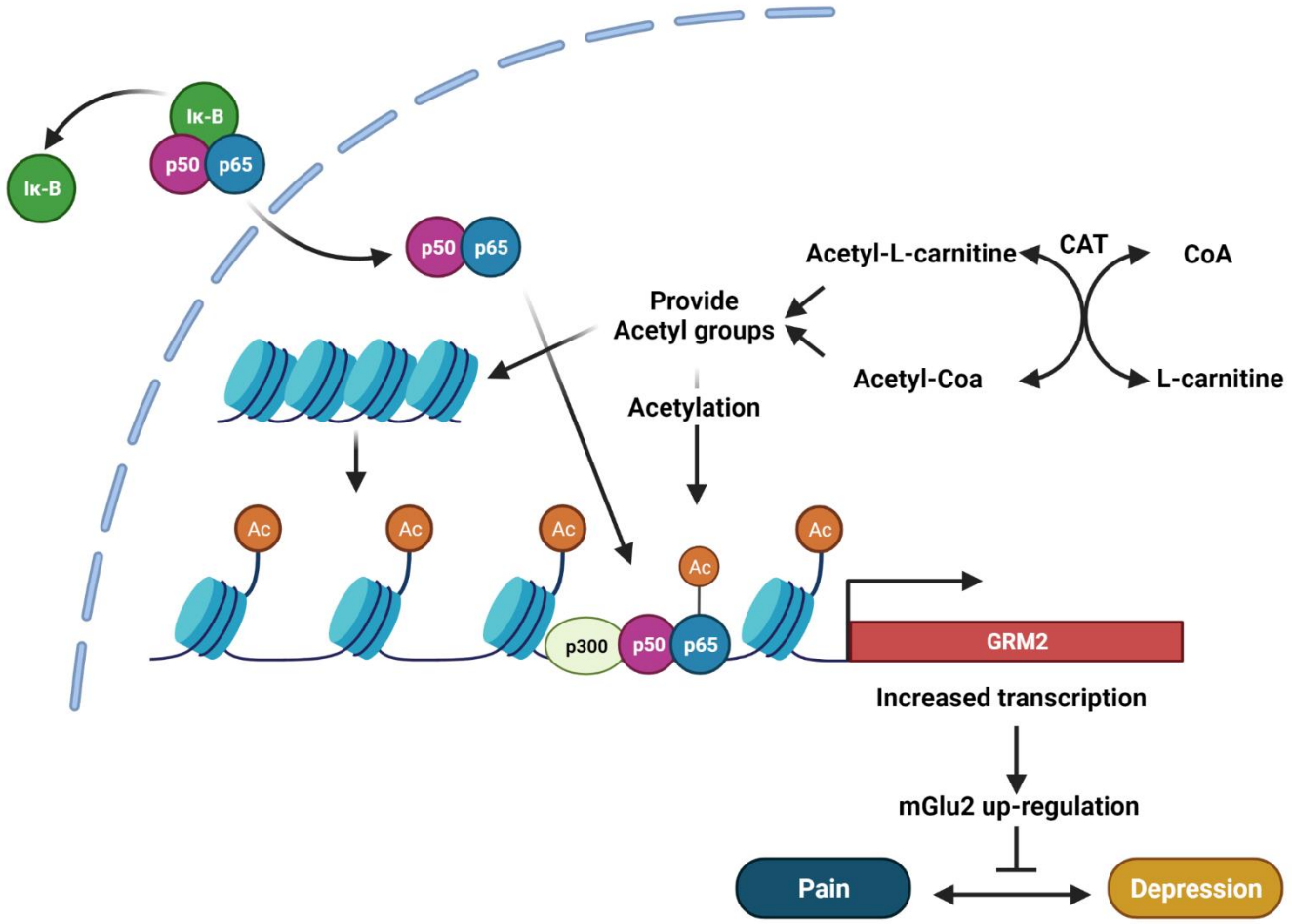
Sarzi-Puttini P *et al.* *Nature Rev Rheumatatol* 2020 16: 645-660



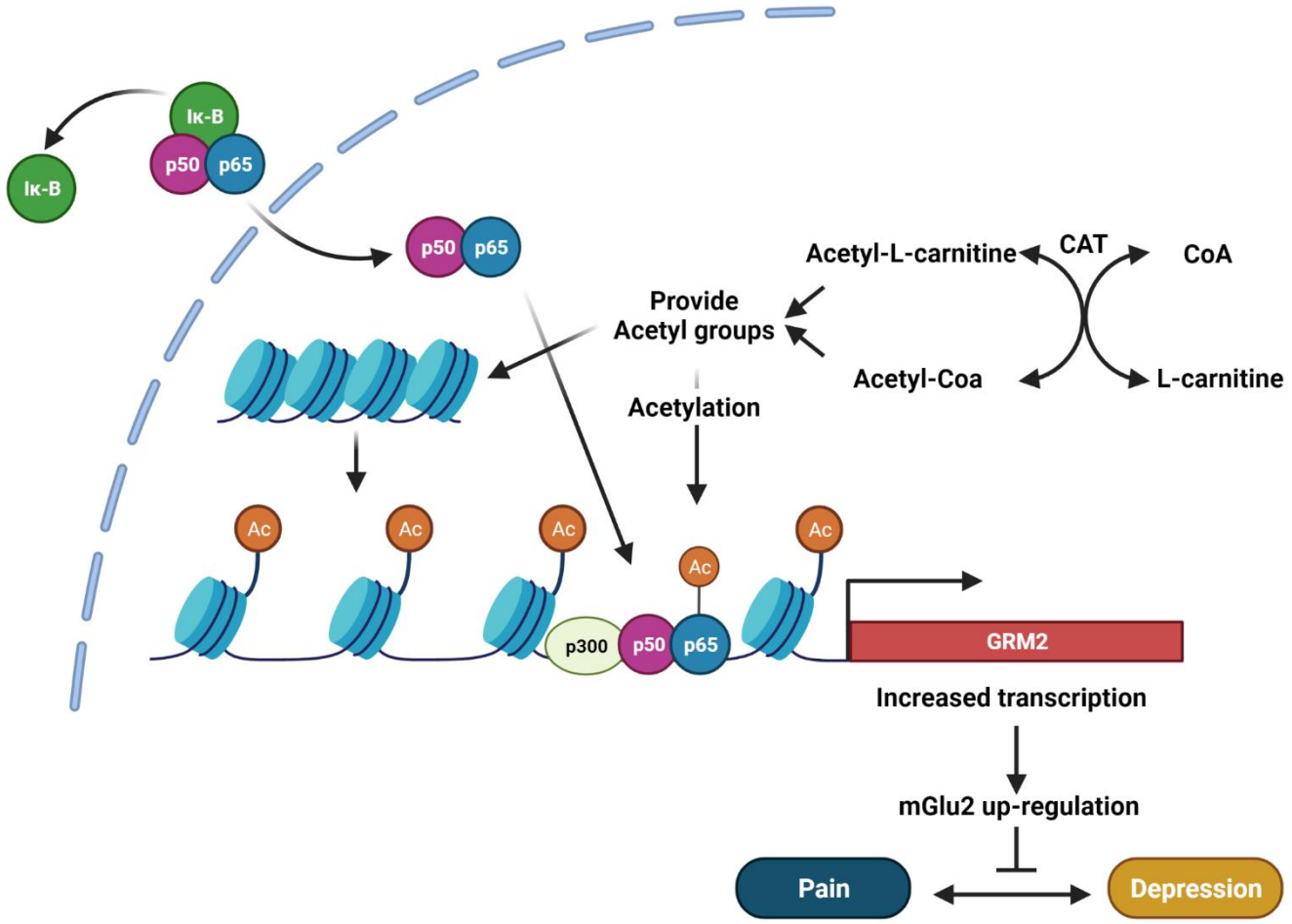
Aumento espressione di circa 10 volte




Primary sensory neuron central terminal
Action potential
Glu
Ca^{2+}
Calcium influx
Glu
Synaptic vesicle release
Neuropeptides
CGRP
Substance P
Na^+
Ca^{2+}
Glu
Glu
Na^+
Glu
NMDA-R
AMPA-R
Voltage-dependent Na^+ and Ca^{2+} influx
mGluR
NK1
CGRP-R
Rapid Na^+ influx
Slow modulatory response
Postsynaptic depolarization
Secondary relay neuron (postsynaptic membrane)
Reach voltage-gated Na^+ channel threshold
Action potential



Pharmacol. Res. 2021 *in press*



Pharmacol. Res. 2021 *in press*