Sociedad Española de Reumatología

El fenómeno de sensibilización periférica en la fibromialgia

¿Qué sabemos actualmente?

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XLV CONGRESO NACIONAL DE LA SER
VALENCIA, 21/24 MAYO 2019

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VALENCIA
21/24 MAYO 2019

Ningún conflicto de intereses relacionado con esta presentación

He recibido financiación en forma de:

- Proyectos de investigación: Esteve, Gebro, Grünenthal
- Honorarios por ponencias: Esteve, Ferrer, Grünenthal, Kern, Kwyova-Kirin
- Participación en Comités de Expertos: Esteve, Gebro, Grünenthal, Kwyova-Kirin
- Actividades docentes: Esteve, Grünenthal, Menarini, Mundipharma

Seminars in Arthritis and Rheumatism 46 (2016) 319–329

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria

Frederick Wolfe, MD[a,b,*], Daniel J. Clauw, MD[c], Mary-Ann Fitzcharles, MD[d], Don L. Goldenberg, MD[e,f], Winfried Häuser, MD[g,h], Robert L. Katz, MD[i], Philip J. Mease, MD[j,k], Anthony S. Russell, MD[l], Irwin Jon Russell, MD, PhD[m], Brian Walitt, MD, MPH[n]

(1) Presencia de dolor generalizado, definido como dolor en, al menos, 4 regiones de 5
(2) Los síntomas llevan manifestándose de forma similar al menos 3 meses
(3) Índice de dolor generalizado (WPI) >7 y un valor en la escala de gravedad de síntomas (SSS) > 5, o WPI de 4-6 y SSS > 9
(4) Un diagnóstico de fibromialgia no invalida otros diagnósticos. Un diagnóstico de fibromialgia no excluye la presencia de otras patologías con relevancia clínica.

*Wolfe y cols., Seminars in Arthritis and Rheumatism **2016**; 46:319-329*

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FIBROMIALGIA

"Factores de confusión"

- Fatiga crónica,
- Síndrome de intestino irritable,
- Dispepsia funcional,
- Alteración temporomandibular,
- Síndrome de dolor miofascial,
- Síndrome de piernas inquietas,
- Cistitis intersticial,
- Síndrome de estrés postraumático,
- .....
- Síndrome de la guerra del Golfo!!!

Síndromes de Sensibilidad Central

*Tsilioni y cols. J Pharmacol Exp Ther **2016**; 356:664–672*
*Yunus. Semin Arthritis Rheum,**2007**; 36:339–356.*
*Theoharides. Clin Ther, **2013**; 35:544–547.*

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IALGIA

Topical Review
PAIN

Do we need a third mechanistic descriptor for chronic pain states?

Eva Kosek[a,*], Milton Cohen[b], Ralf Baron[c], Gerald F. Gebhart[d], Juan-Antonio Mico[e], Andrew S.C. Rice[f], Winfried Rief[g], A. Kathleen Sluka[h]

3.2. When should the descriptor be used and when not?

The descriptor is primarily intended for patients suffering from chronic pain conditions characterized by evidence of altered nociceptive processing, such as those currently labelled as fibromyalgia,[2] CRPS,[47] nonspecific chronic low-back pain,[16] irritable bowel syndrome,[39] and other "functional" visceral pain disorders.[8,48] In addition, patients suffering initially from nociceptive pain, such as osteoarthritis, may develop alterations in nociceptive processing manifested as altered descending pain inhibition[3,28] accompanied by spread of hypersensitivity.[2,17,29] These patients would then be considered to have a combination of nociceptive and "nociplastic/algopathic/nocipathic" contributors to their pain. The new descriptor is intended to distinguish patients suffering from conditions where altered nociception has been documented from those where the pain mechanisms are still truly unknown. Therefore, the new descriptor does not apply to patients reporting pain without hypersensitivity. As such, it is neither a synonym for idiopathic pain or pain of unknown origin nor a label awarded by exclusion.

Kosek y cols., Pain. ***2016****; 157:1382-6*

- **DOLOR NOCIPLÁSTICO**:

Es aquel dolor que surge de la nocicepción alterada a pesar de que no hay evidencia clara de daño tisular real o potencial que cause la activación de nociceptores periféricos o evidencia de enfermedad o lesión del sistema somatosensorial que causa dolor.

SENSIBILIZACIÓN PERIFÉRICA

Sensibilización*

Respuesta aumentada de las neuronas nociceptivas a estímulos normales, o presencia de respuesta a estímulos sub-umbrales

Nota: La sensibilización puede incluir una bajada en el umbral y un aumento en la respuesta al estímulo. Pueden aparecer descargas espontáneas y aumento del campo receptorial. Se trata de un término neurofisiológico que sólo puede aplicarse cuando el *input* y el *output* de un sistema neuronal concreto está siendo analizado, es decir si se puede controlar el estímulo y valorar (medir) la respuesta.

Clínicamente, la sensibilización sólo puede inferirse por fenómenos como la alodinia o la hiperalgesia.

Sensibilización periférica*

Respuesta aumentada y reducción del umbral de respuesta de las neuronas nociceptivas de la periferia cuando se estimulan sus campos receptivos.

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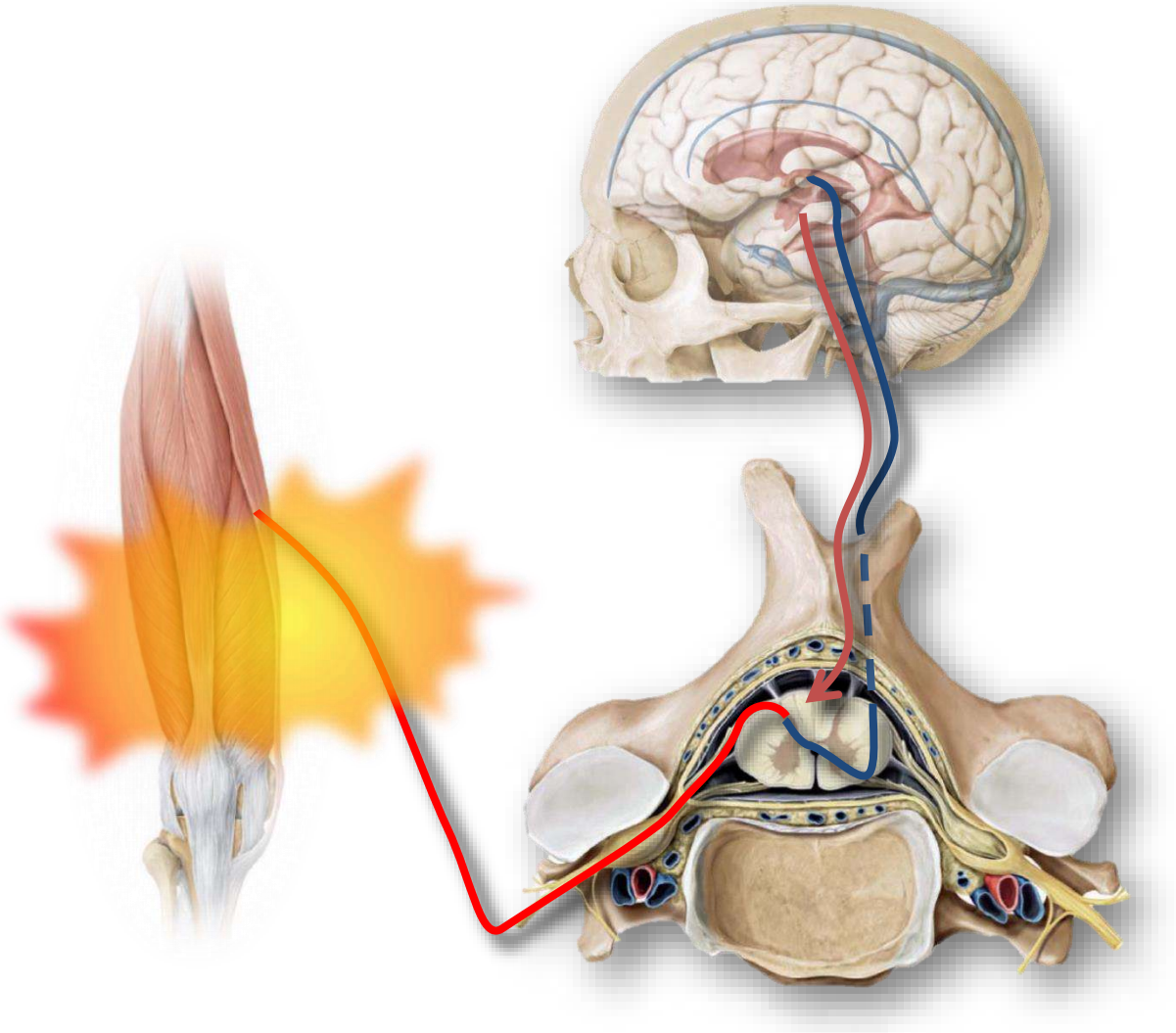
SENSIBILIZACIÓN PERIFÉRICA

- **Inflamación**: Aumento de citocinas y mediadores proinflamatorios …y más dolor
- **Fibrosis**: Aumento del colágeno, mayor tensión del tejido…. y más dolor.
- **Degradación tisular**: Aumento de metaloproteasas, más lesiones tisulares….y más dolor.
- Aumento de **neurotransmisores** (Sustancia P, CGRP) actividad ganglionar y medular…y más dolor



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SENSIBILIZACIÓN PERIFÉRICA

- **Inflamación**: Aumento de citocinas y mediadores proinflamatorios …y más dolor
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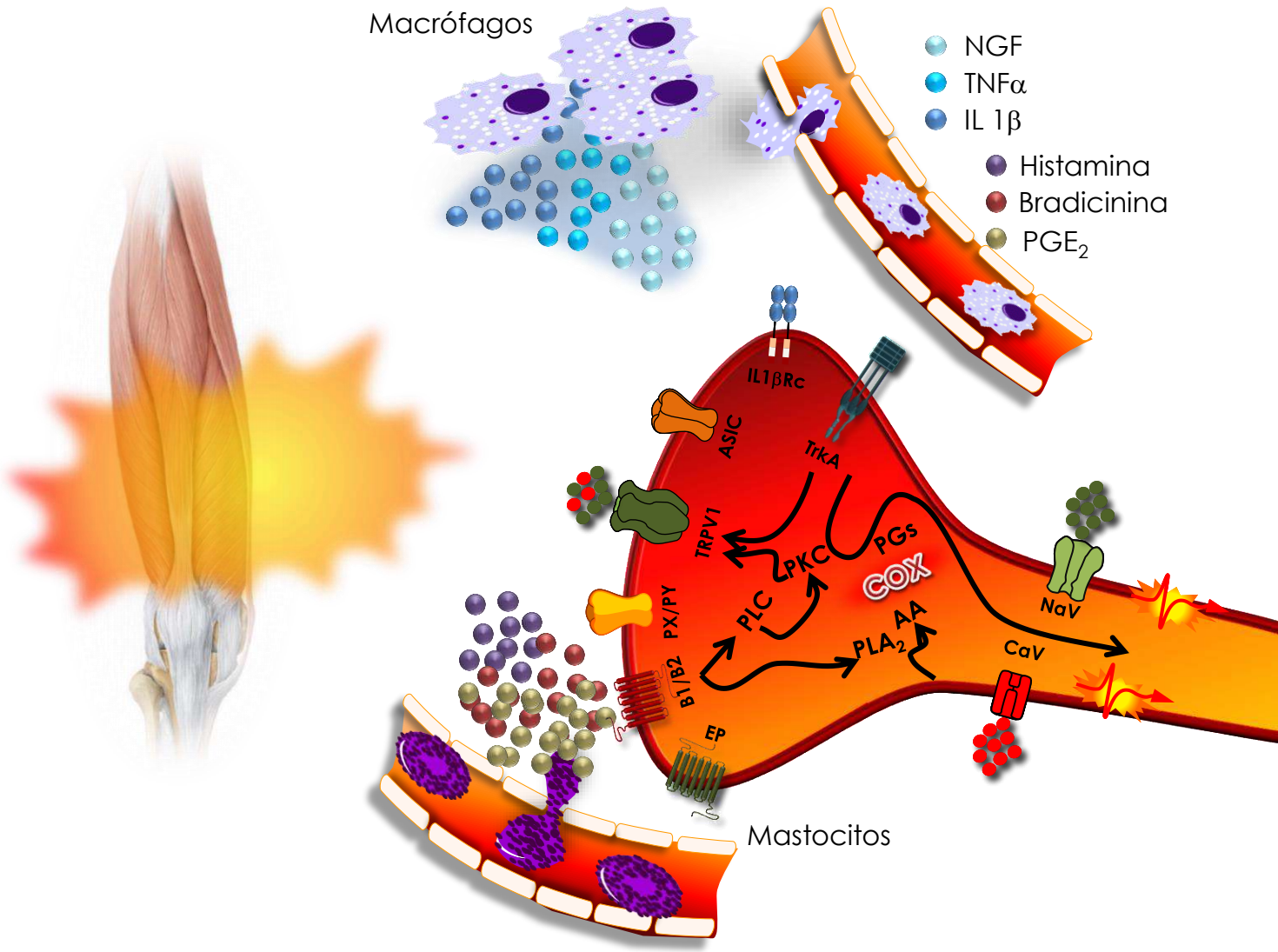

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Miller y cols., Cytokine. 2014; 70: 185-193.
Kapoor y cols., Nat Rev Rheumatol 2011; 7: 33-42

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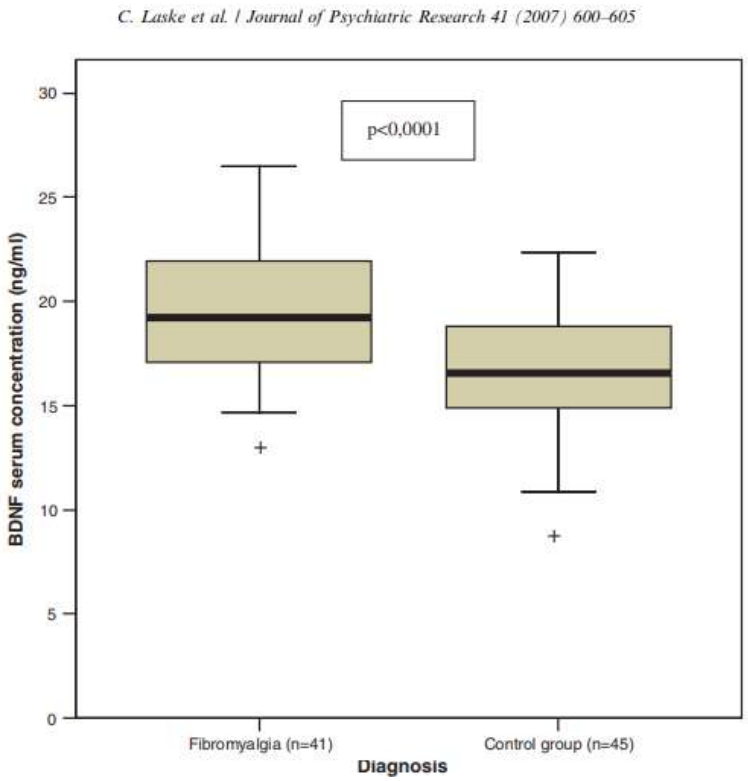
Available online at www.sciencedirect.com
ScienceDirect
Journal of Psychiatric Research 41 (2007) 600–605
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants

Christoph Laske [a,*], Elke Stransky [a], Gerhard W. Eschweiler [a,b], Reinhild Klein [c], Andreas Wittorf [a], Thomas Leyhe [a,b], Elke Richartz [a], Niklas Köhler [a], Matthias Bartels [a], Gerhard Buchkremer [a], Klaus Schott [a]

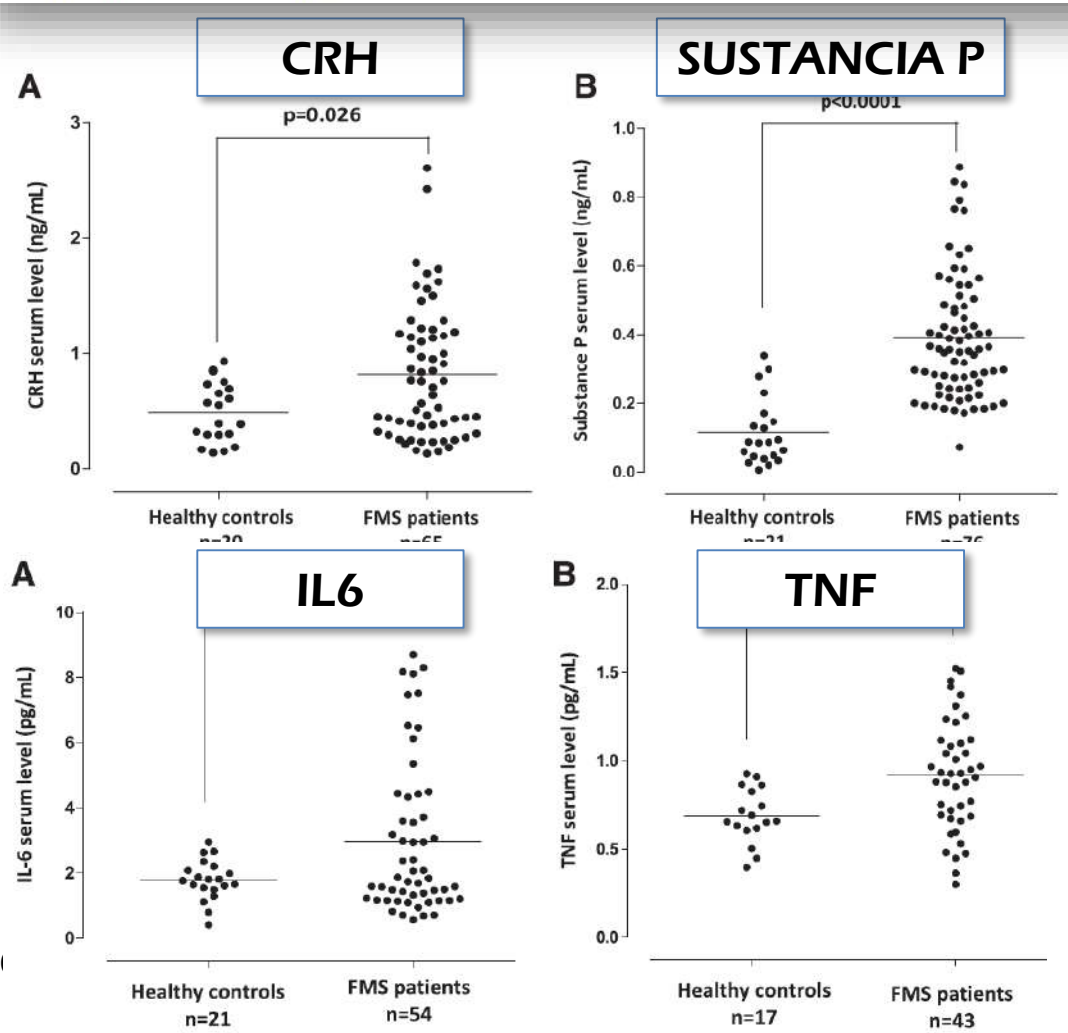


1521-0103/356/3/664–672$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.115.230060
J Pharmacol Exp Ther 356:664–672, March 2016

Neuropeptides CRH, SP, HK-1, and Inflammatory Cytokines IL-6 and TNF Are Increased in Serum of Patients with Fibromyalgia Syndrome, Implicating Mast Cells

Irene Tsilioni, Irwin J. Russell, Julia M. Stewart, Rae M. Gleason, and Theoharis C. Theoharides



Laske y cols., J Psychiatric Res. ***2007****; 41:600-605*

Tsiolioni y cols., JPET. ***2016****; 356:464-472*

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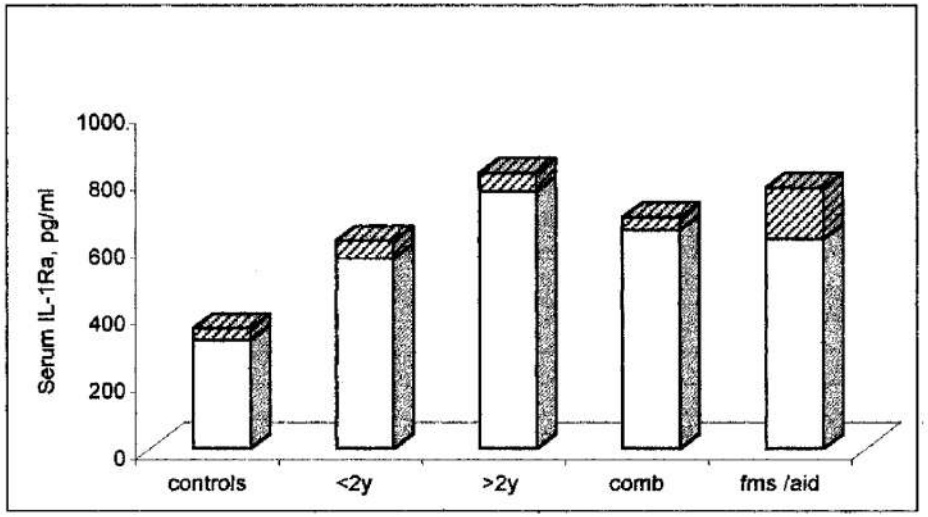
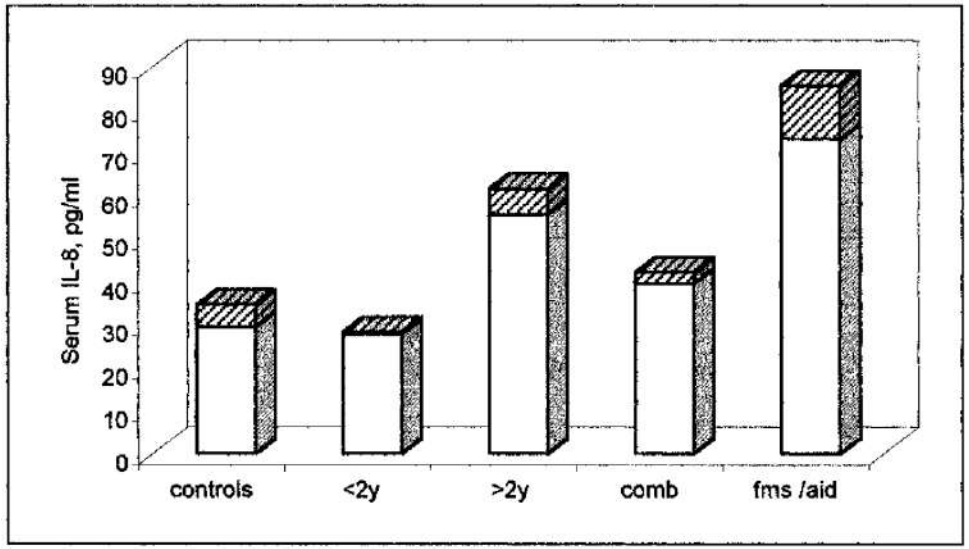
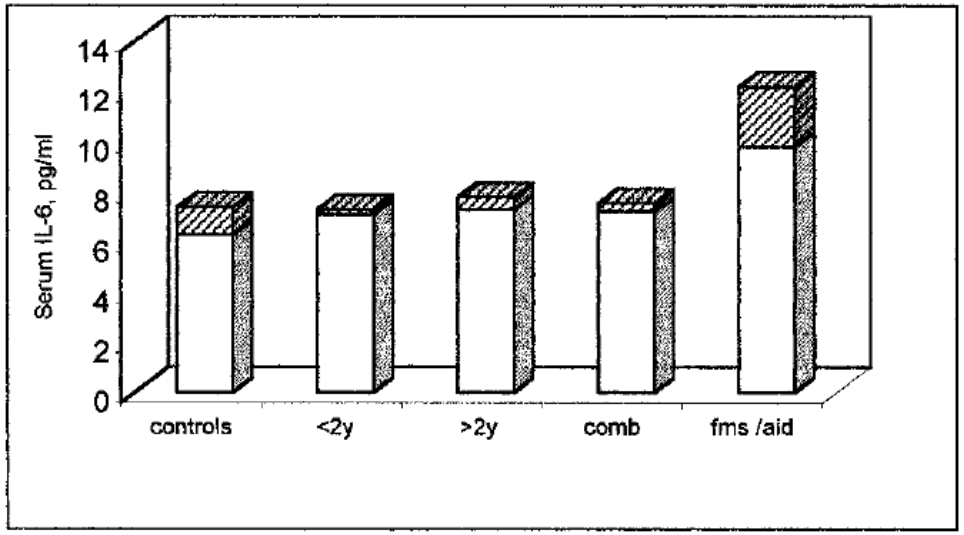
Rheumatology 2001;40:743–749

Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study

D. J. Wallace, M. Linker-Israeli, D. Hallegua, S. Silverman, D. Silver and M. H. Weisman







*Wallace y cols., Reumatology, **2001**; 40: 743-749*

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Modelos animales para el estudio del Dolor y de la Fibromialgia

- ✓ Estímulo térmico del cola (“Tail flick test”): D’Amour y Smith, 1941
- ✓ Test de la placa caliente (“Hot-plate test”): Woolfe y MacDonald, 1944
- ✓ Test de presión de la pata (“Randall–Selitto’s test”): Randall y Selitto, 1957
- ✓ Test de la formalina (“Formalin test”): Dubuisson y Dennis, 1977

- ✓ Modelo de artritis, por administración de Coadyuvante de Freund: Walz y cols., 1971
- ✓ Modelo de dolor neuropático periférico, por ligadura de nervio espinal: Bennett y Xie, 1988
- ✓ Modelo de artrosis, por administración de MonolodoAcetato: Guingamp y cols., 1997

- ✓ Modelos de Fibromialgia:
  - ✓ Inyección de salino hipertónico (Sluka y cols., 2001)
  - ✓ Estrés por sonido (Khasar y cols., 2005)
  - ✓ Estrés por frío (Nishiyori y Ueda, 2008)
  - ✓ Depleción de monoaminas biógenas por reserpina (Nagaura y cols., 2009)

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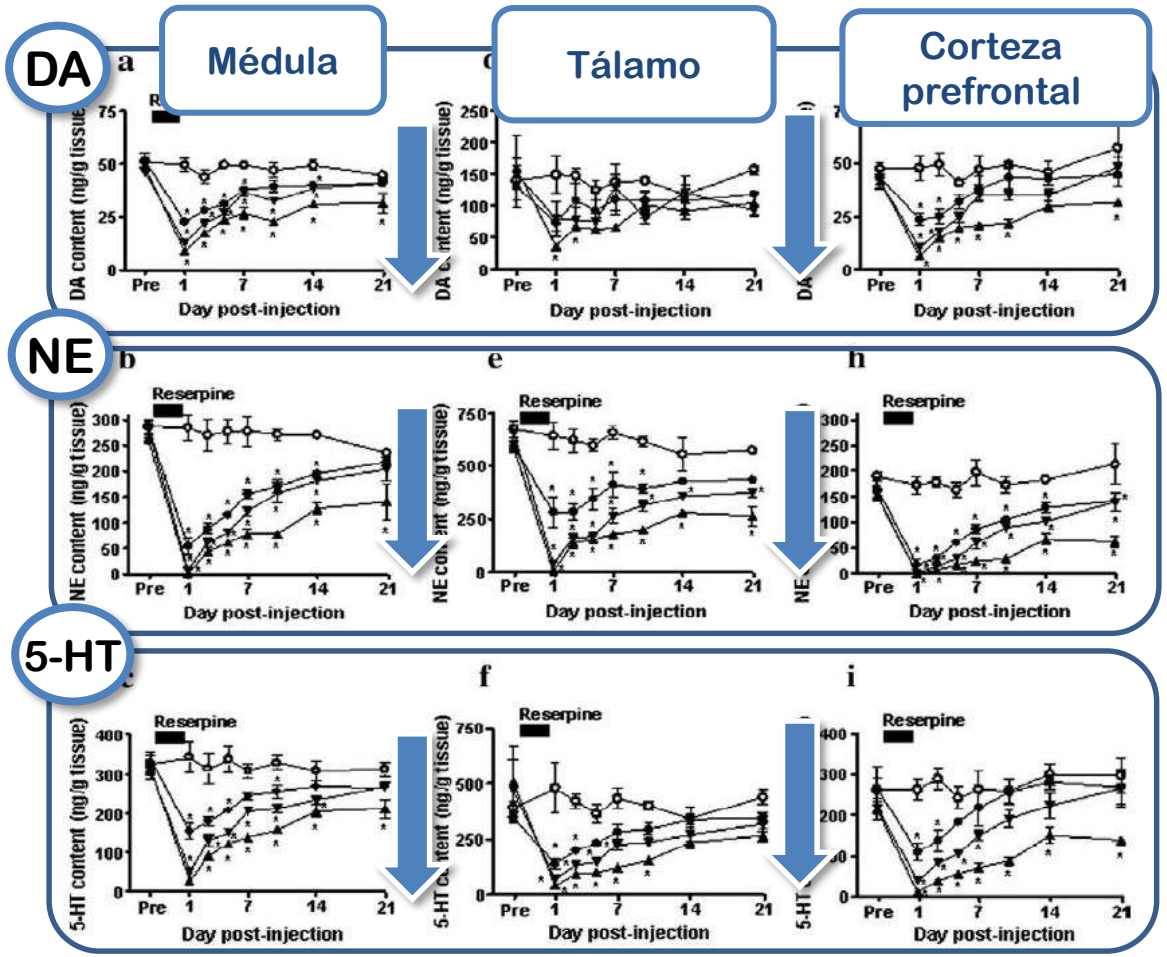
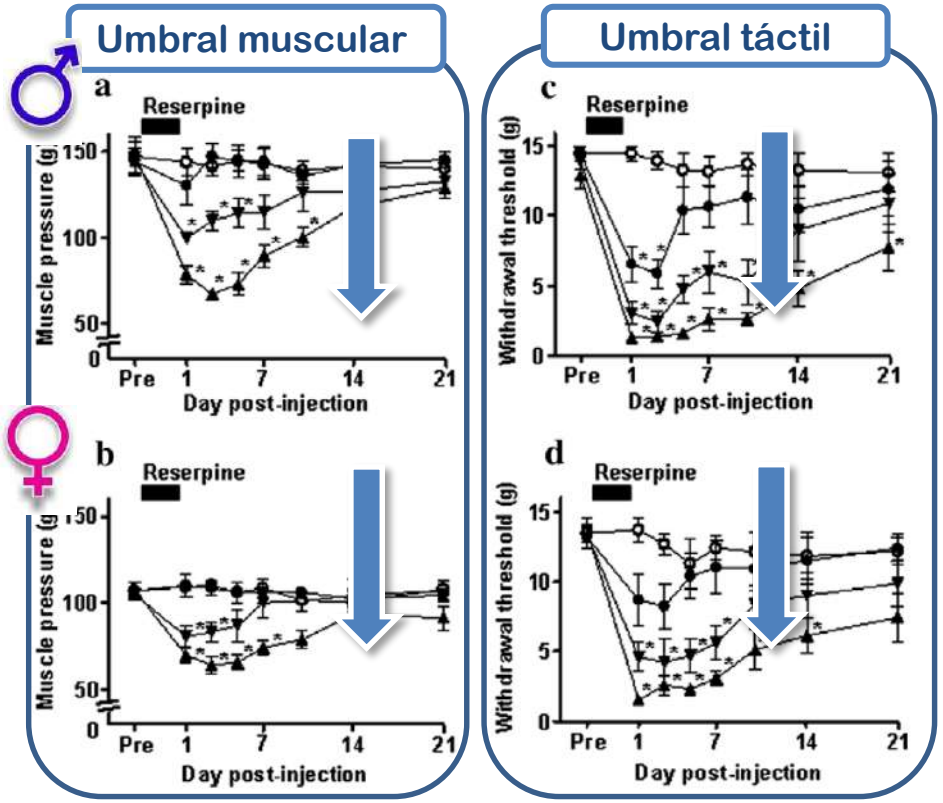
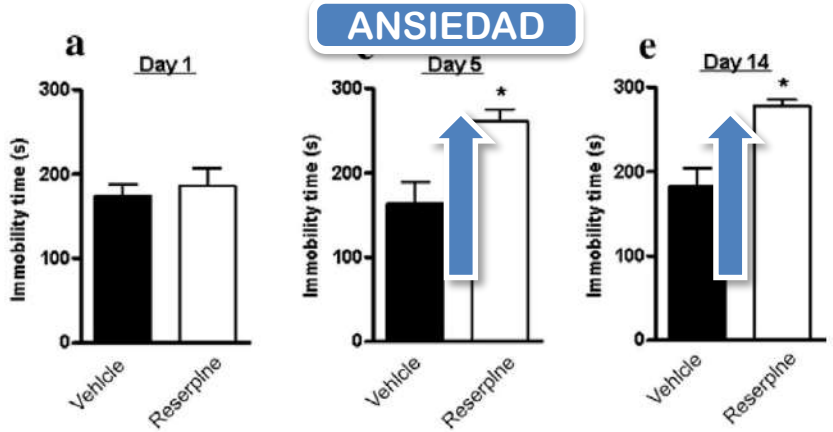
IASP
PAIN® 146 (2009) 26–33
PAIN®
www.elsevier.com/locate/pain

Biogenic amine depletion causes chronic muscular pain and tactile allodynia accompanied by depression: A putative animal model of fibromyalgia

Yukinori Nagakura *,[1], Tomoya Oe [1], Toshiaki Aoki, Nobuya Matsuoka
Pharmacology Research Labs., Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan







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*Nagakura y cols., Pain **2009**; 146: 26-33*

Behavioural Brain Research 226 (2012) 242–249

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

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

Research report

Different pathophysiology underlying animal models of fibromyalgia and neuropathic pain: Comparison of reserpine-induced myalgia and chronic constriction injury rats

Yukinori Nagakura[a,*], Masayasu Takahashi[a], Takahisa Noto[b], Toshihiro Sekizawa[a], Tomoya Oe[a], Eiji Yoshimi[a], Keisuke Tamaki[a], Yasuaki Shimizu[a]

[a] Department of Pain Research, Pharmacology Research Labs, Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan
[b] Drug Safety Research Labs, Drug Discovery Research, Astellas Pharma Inc., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan

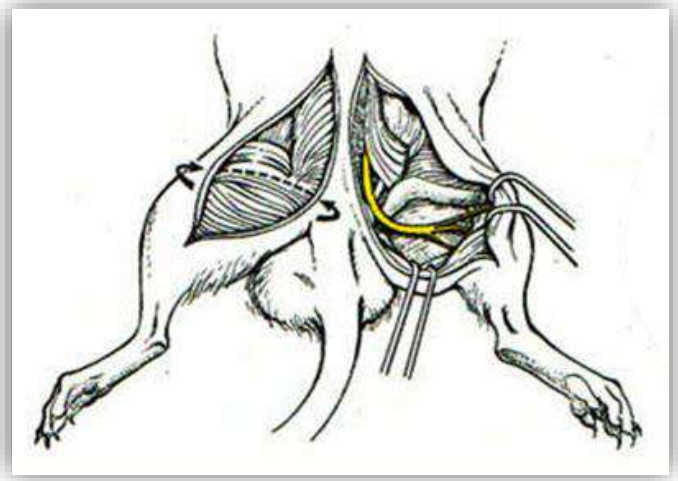

Table 2
Features of reserpine-induced myalgia (RIM) and chronic constriction injury (CCI) rat.

	RIM rat	CCI rat
Induction of pain	Reserpine injection	Fiber injury in the sciatic nerve
Pain symptomatic phenotypes	Chronic hypersensitivity to tactile, cold, and muscle pressure stimuli.	Chronic hypersensitivity to tactile, cold, thermal, and paw pressure stimuli [5,21,32]
Histopathology		
Supra-spinal	Slight vacuolar change in the substantia nigra	No apparent change
Spinal	No apparent change	Upregulation of GFAP signal
Peripheral	No apparent change	Degeneration of the dorsal root ganglia and sciatic nerve fibers
Responsiveness to drug (mexiletine) therapy	Insensitive	Sensitive
Primary mechanism of pain	Dysfunctional pain control network in the brain including the substantia nigra	Neuronal plastic change at the level of peripheral neuron and spinal cord
Relevant pain conditions	Patients with attenuation of pain control system in the brain without apparent organic disorder (e.g., fibromyalgia)	Patients with peripheral neuropathy (e.g., complex regional pain syndrome)

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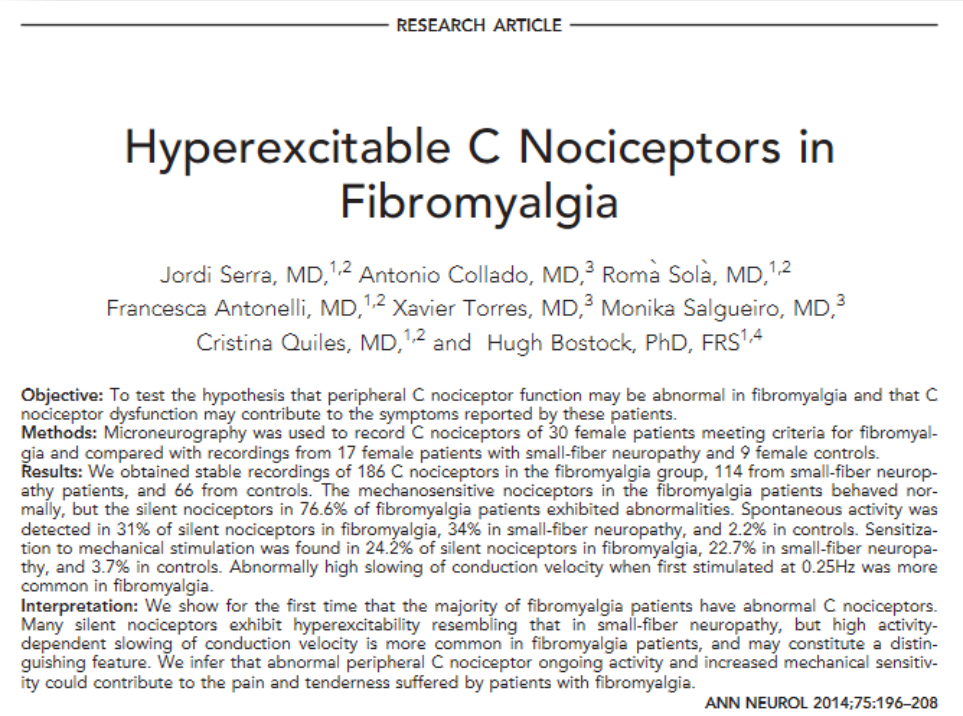
*Nagakura y cols., Behav Brain Res **2012**; 226: 242-249*



RESEARCH ARTICLE

Hyperexcitable C Nociceptors in Fibromyalgia

Jordi Serra, MD,[1,2] Antonio Collado, MD,[3] Romà Solà, MD,[1,2]
Francesca Antonelli, MD,[1,2] Xavier Torres, MD,[3] Monika Salgueiro, MD,[3]
Cristina Quiles, MD,[1,2] and Hugh Bostock, PhD, FRS[1,4]

Objective: To test the hypothesis that peripheral C nociceptor function may be abnormal in fibromyalgia and that C nociceptor dysfunction may contribute to the symptoms reported by these patients.
Methods: Microneurography was used to record C nociceptors of 30 female patients meeting criteria for fibromyalgia and compared with recordings from 17 female patients with small-fiber neuropathy and 9 female controls.
Results: We obtained stable recordings of 186 C nociceptors in the fibromyalgia group, 114 from small-fiber neuropathy patients, and 66 from controls. The mechanosensitive nociceptors in the fibromyalgia patients behaved normally, but the silent nociceptors in 76.6% of fibromyalgia patients exhibited abnormalities. Spontaneous activity was detected in 31% of silent nociceptors in fibromyalgia, 34% in small-fiber neuropathy, and 2.2% in controls. Sensitization to mechanical stimulation was found in 24.2% of silent nociceptors in fibromyalgia, 22.7% in small-fiber neuropathy, and 3.7% in controls. Abnormally high slowing of conduction velocity when first stimulated at 0.25Hz was more common in fibromyalgia.
Interpretation: We show for the first time that the majority of fibromyalgia patients have abnormal C nociceptors. Many silent nociceptors exhibit hyperexcitability resembling that in small-fiber neuropathy, but high activity-dependent slowing of conduction velocity is more common in fibromyalgia patients, and may constitute a distinguishing feature. We infer that abnormal peripheral C nociceptor ongoing activity and increased mechanical sensitivity could contribute to the pain and tenderness suffered by patients with fibromyalgia.

ANN NEUROL 2014;75:196–208

- "En pacientes con fibromialgia, hay modificaciones en las conductas de las fibras C: los mecanonociceptores se comportan normalmente, pero los silentes muestran actividad espontánea."
- "Se evidencia una sensibilización a la estimulación mecánica en 24% de los nociceptores silentes."

"Concluimos que la <u>actividad anormal de los nociceptores C</u> periféricos y el aumento de la sensibilidad mecánica puede contribuir al dolor y sensibilidad en pacientes con fibromalgia"

*Serra y cols., Ann Neurol **2014**; 75: 196-208*

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Research Paper
PAIN
T. Taguchi et al. • 156 (2015) 415–427

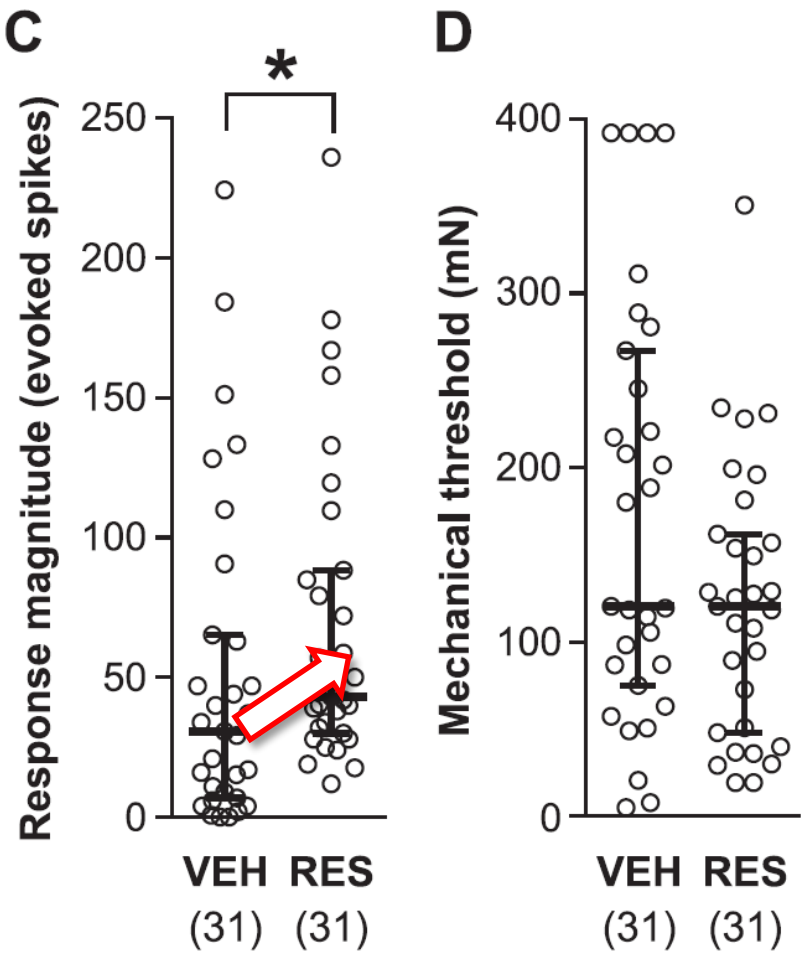
Peripheral and spinal mechanisms of nociception in a rat reserpine-induced pain model

Toru Taguchi[a,*], Kimiaki Katanosaka[a,d], Masaya Yasui[b], Koei Hayashi[a], Mai Yamashita[a], Koji Wakatsuki[a], Hiroshi Kiyama[b], Akihiro Yamanaka[a], Kazue Mizumura[c]

March 2015 • Volume 156 • Number 3

Receptor types of C-fibers electrically identified in series 1 (A) and mechanoresponsive C-nociceptors in series 1 and 2 combined (B).

	Vehicle number (%)	Reserpine number (%)	*P*
(A) Electrically identified C-fibers (series 1)			
Mech (+) nociceptor	28 (38.4)	17 (14.3)	*
Mechanoinsensitive	27 (37.0)	71 (59.7)	†
CLTM	3 (4.1)	3 (2.5)	NS
Presumed sympathetic	15 (20.5)	28 (23.5)	NS
Total	73 (100)	119 (100)	
(B) Mechanoresponsive C-nociceptors (series 1 + 2)			
CM	4 (13.3)	4 (13.3)	NS
CMC	4 (13.3)	2 (6.7)	NS
CMH	16 (53.3)	20 (66.7)	NS
CMCH	6 (20.0)	4 (13.3)	NS
Total	30 (100)	30 (100)	



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*Taguchi y cols., Pain **2015**; 156: 415-427*

Seminars in Arthritis and Rheumatism 48 (2019) 933–940

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

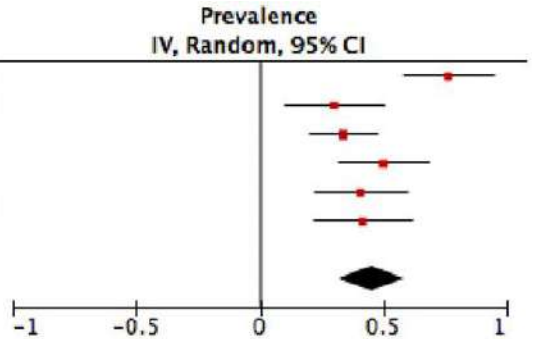
journal homepage: www.elsevier.com/locate/semarthrit

A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis

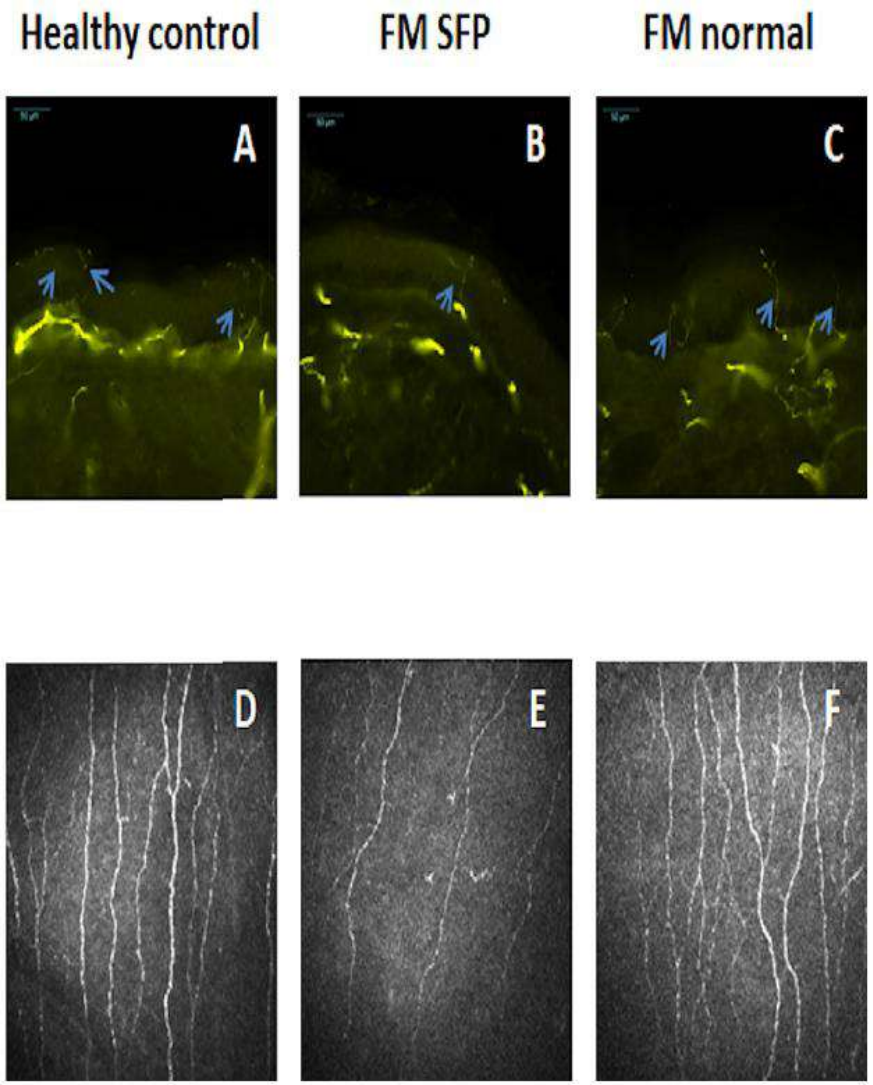
Rebecca Grayston[a], Gabriela Czanner[a,b], Kareim Elhadd[c], Andreas Goebel[d], Bernhard Frank[d], Nurcan Üçeyler[e], Rayaz A Malik[f], Uazman Alam[a,g,h,i,*]

Study or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI
de Tommaso, 2014	0.762	0.093	16.6%	0.76 [0.58, 0.94]
Giannoccaro, 2014	0.3	0.102	15.6%	0.30 [0.10, 0.50]
Kosmidis, 2014	0.337	0.07	19.2%	0.34 [0.20, 0.47]
Leinders, 2016	0.5	0.094	16.5%	0.50 [0.32, 0.68]
Oaklander, 2013	0.407	0.095	16.4%	0.41 [0.22, 0.59]
Uceyler, 2013	0.417	0.101	15.7%	0.42 [0.22, 0.61]
Total (95% CI)			**100.0%**	**0.45 [0.32, 0.59]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.60$, df = 5 (P = 0.005); $I^2 = 70\%$
Test for overall effect: Z = 6.66 (P < 0.00001)



:howing prevalence estimates of SFP in fibromyalgia in studies using skin biopsies. de Tommaso et al. [51]; Giannoccaro et al. [28]; Kosmidis
:r et al. [27] and Üçeyler et al. [26].



*R. Grayston et al. / Seminars in Arthritis and Rheumatism 48 (**2019**) 933940*

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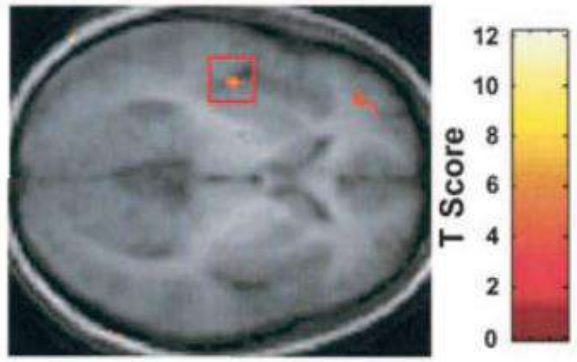
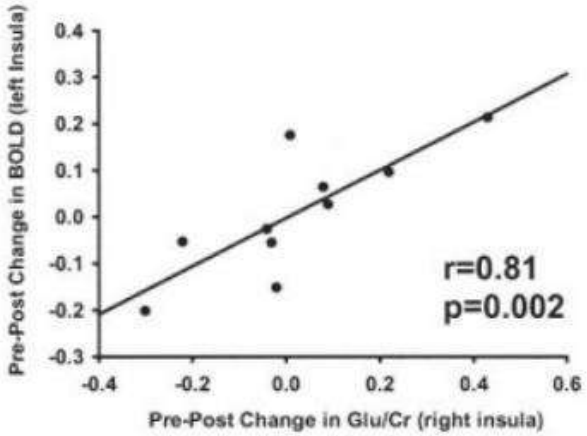
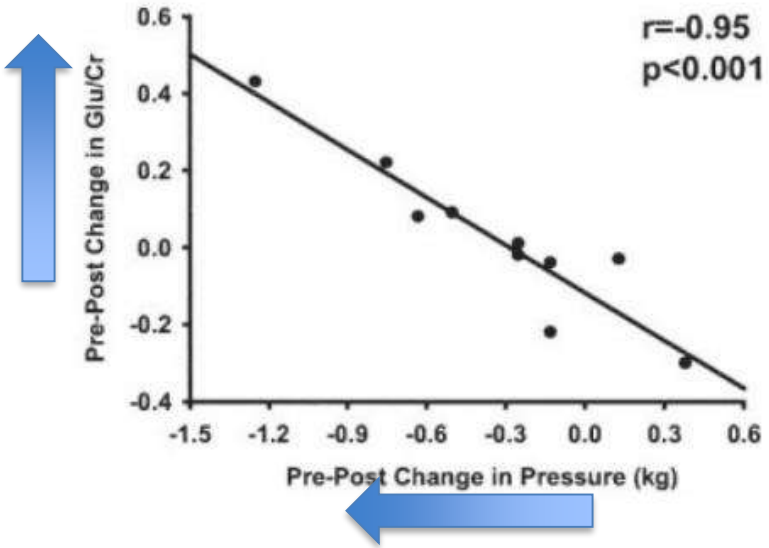
ARTHRITIS & RHEUMATISM
Vol. 58, No. 3, March 2008, pp 903–907
DOI 10.1002/art.23223

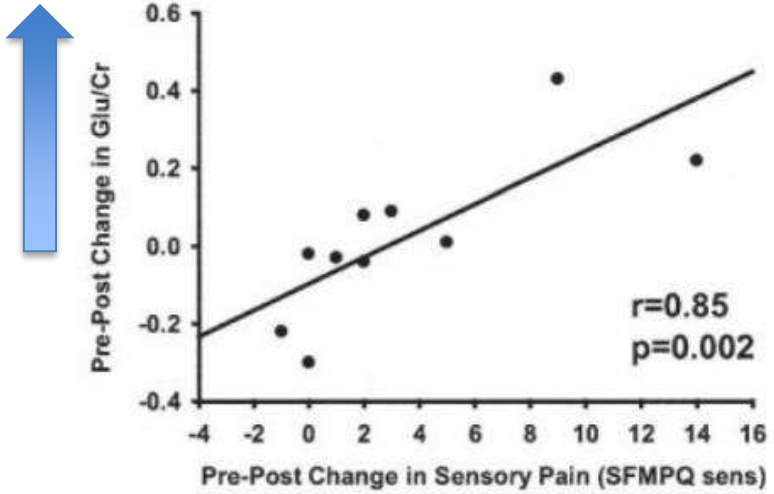
Dynamic Levels of Glutamate Within the Insula Are Associated With Improvements in Multiple Pain Domains in Fibromyalgia

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Michael Hsu, Myria Petrou, Seong-Ho Kim, Samuel A. McLean, Richard H. Gracely, and Daniel J. Clauw









Harris y cols., Arthr & Rheum. ***2008****; 58: 903-907*

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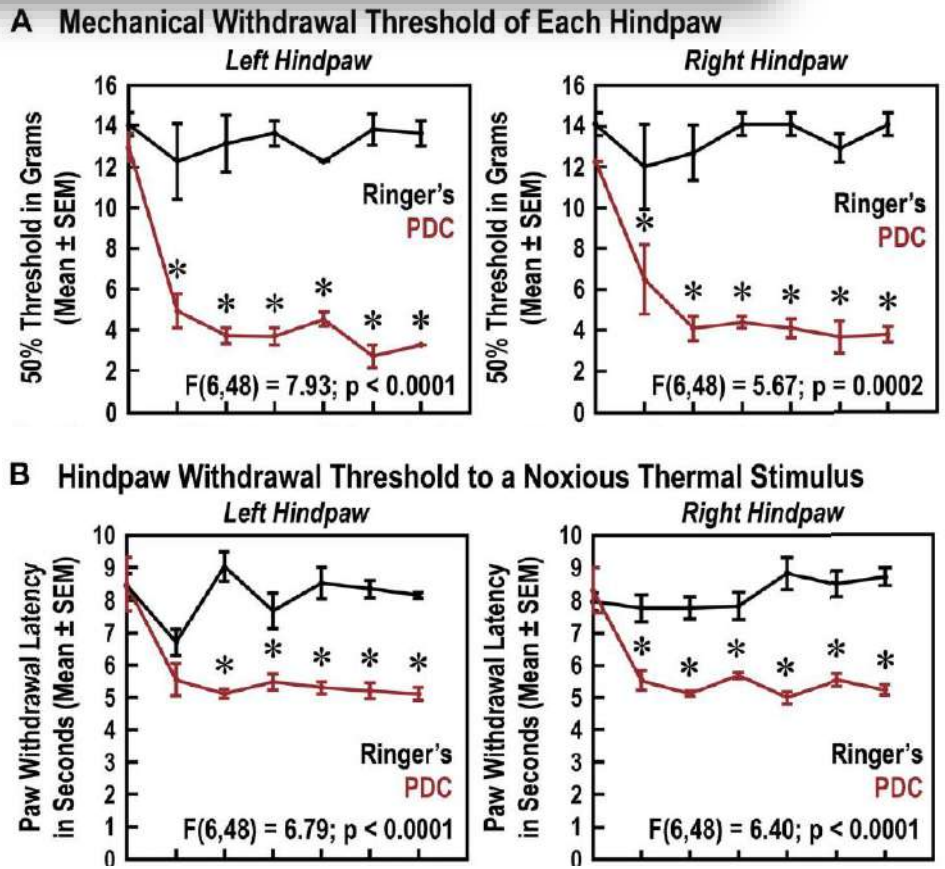
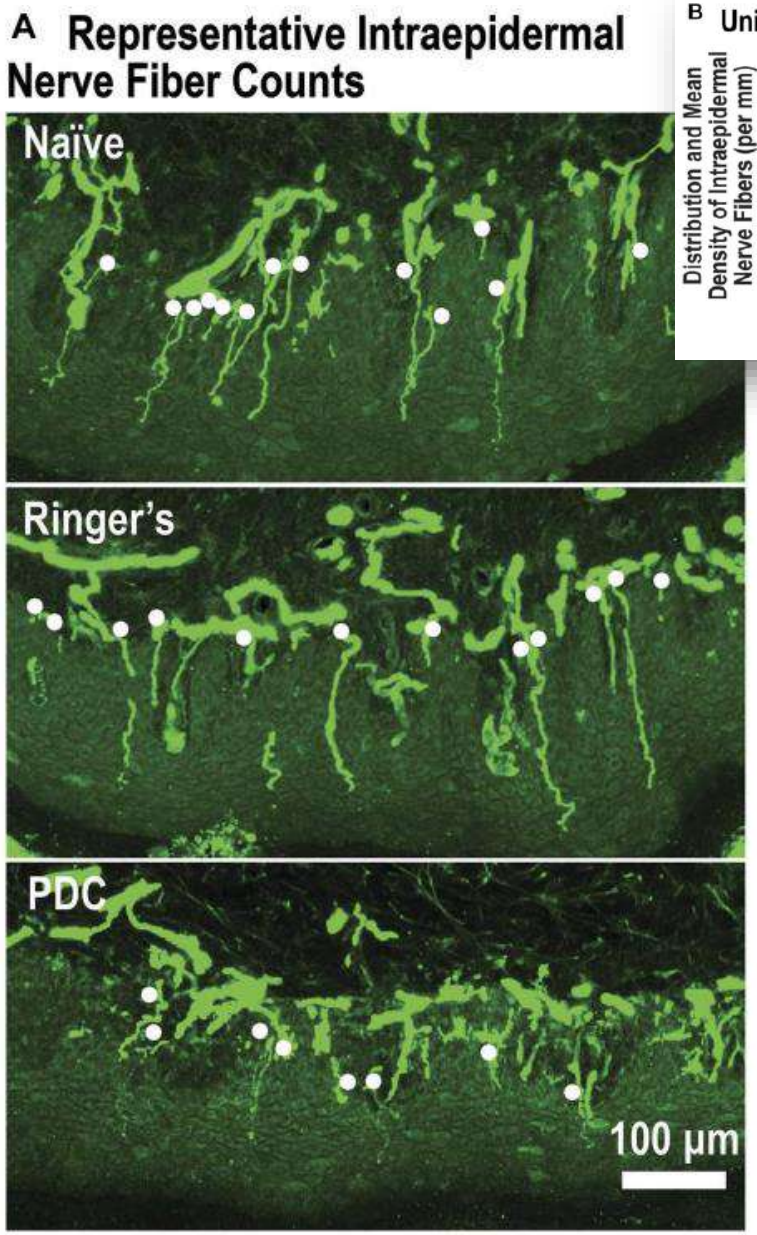
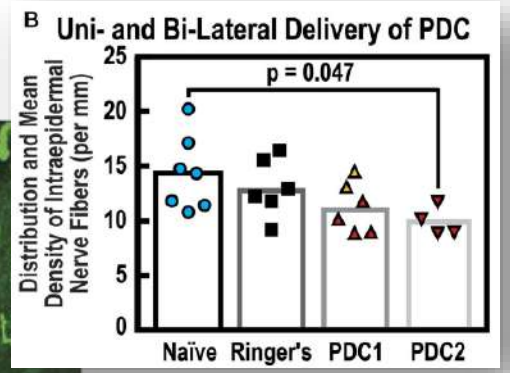
Basic Science
Brief Report
OPEN
PAIN REPORTS

Reduced intraepidermal nerve fiber density after a sustained increase in insular glutamate: a proof-of-concept study examining the pathogenesis of small fiber pathology in fibromyalgia

Steven E. Harte[a], Daniel J. Clauw[a], John M. Hayes[b], Eva L. Feldman[b], Irene C. St Charles[a], Christopher J. Watson[a,*]







Harte y cols., Pain Rep. ***2017;*** *2(3):e590.*

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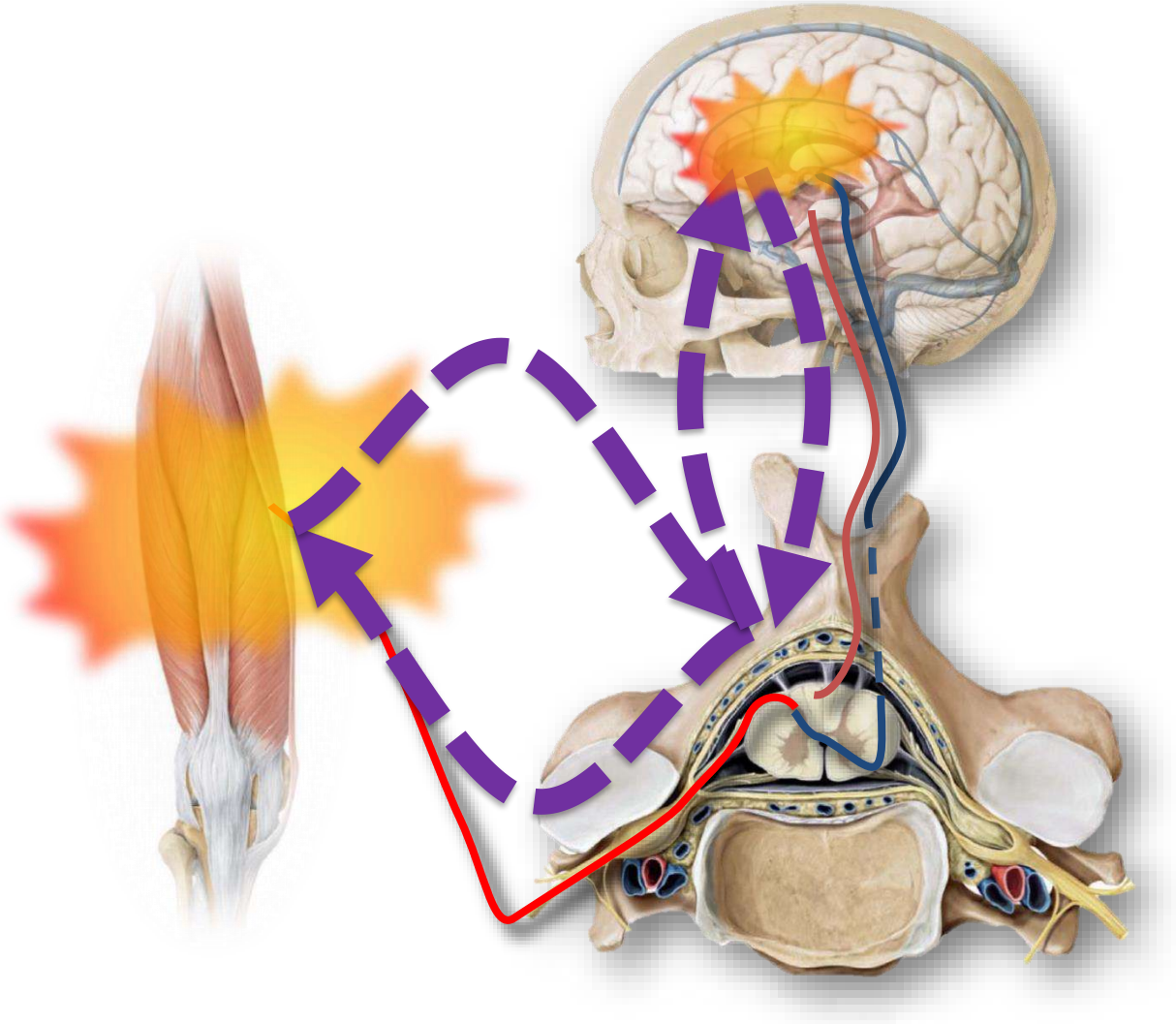
SENSIBILIZACIÓN PERIFÉRICA
….y FIBROMIALGIA

- **Inflamación**: Aumento de citocinas y mediadores proinflamatorios …y más dolor
- **Fibrosis**: Aumento del colágeno, mayor tensión del tejido…. y más dolor.
- **Degradación tisular**: Aumento de metaloproteasas, más lesiones tisulares….y más dolor.
- Aumento de **neurotransmisores** (Sustancia P, CGRP) actividad ganglionar y medular…y más dolor



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El fenómeno de sensibilización periférica en la fibromialgia

¿Qué sabemos actualmente?

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Muchas gracias!

XLV CONGRESO NACIONAL DE LA SER
VALENCIA, 21/24 MAYO 2019