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EVIDENCE BASED, CLINICALLY INTUITIVE CE

Grand Rounds – Pre-Game Warm Up

Why Pain is Not Mechanical or Inflammatory

Presented by: **James Demetrious, DC, DABCO**

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James Demetrious, DC, DABCO

Clinician

- Active Practice >38 years
- Diplomate, American Board of Chiropractic Orthopedists
- Diplomate, International Academy of Neuromusculoskeletal Medicine

Publications

- Over 31 Peer-Reviewed chiropractic journal articles.
- Many Contributions to NCMIC Examiner and Podcast

Educator

- Post-Grad. > 24 years
- NCMIC Speakers' Bureau for>10 years
- Northeast College of Health Sciences
- **PostGradDC**

Editorial

- Editorial Reviewer for journals *Spine*, *Annals of Internal Medicine*, and *Clinical Anatomy*
- Former Managing Editor of *Journal of Chiropractic Orthopedists*

Honors

- Academy of Chiropractic Orthopedists Distinguished Service and Fellow Awards
- American College of Chiropractic Orthopedists Outstanding Achievement Award

Community

- Lower Cape Fear Hospice, Board Member
- Founder, Past-President Wilmington Autism Society
- Optimists Club – Safety Officer

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Purpose...


Cochrane Library

Cochrane Database of Systematic Reviews

Non-pharmacological and non-surgical treatments for low back pain in adults: an overview of Cochrane reviews (Review)

Rizzo RRN, Cashin AG, Wand BM, Ferraro MC, Sharma S, Lee H, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH

Authors' conclusions

Spinal manipulation probably makes no difference to function compared to placebo for people with acute/subacute LBP. Acupuncture probably improves function slightly for people with chronic LBP, compared to sham acupuncture. There is probably no difference between traction and sham traction for pain intensity in people with chronic LBP. Compared to advice to rest, advice to stay active probably reduces pain intensity slightly and improves function slightly for people with acute LBP.

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Purpose!

March 29, 2025 PostGradDC No Comments

Protecting Chiropractic

Written by: James Demetrious, DC, DABCO

Board Certified Chiropractic Orthopedist

- **Chiropractic is Under Attack…Again**
  1. Industry Funding and Conflicts of Interest
  2. Selection Bias in Included Studies
  3. Over-Reliance on RCTs
  4. Author Bias or Ideological Influence
  5. Inconsistencies in Quality
  6. Slow Updating of Reviews
  7. Bias Through Omission

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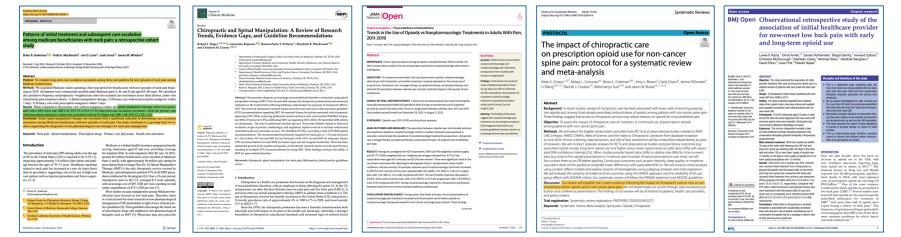
Highly powered research confirms the benefit of CHIROPRACTIC.



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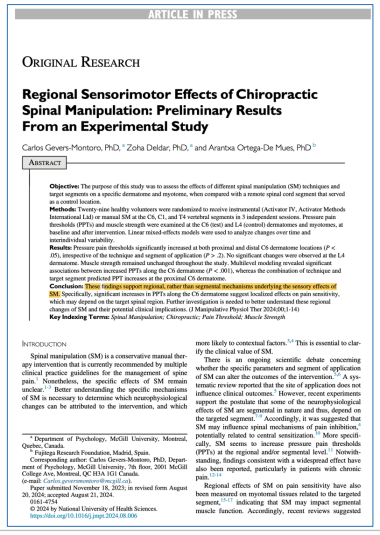
How Do We Shine Above All Other?



ARTICLE IN PRESS

ORIGINAL RESEARCH

Regional Sensorimotor Effects of Chiropractic Spinal Manipulation: Preliminary Results From an Experimental Study

Carlos Gevers-Montoro, PhD,[a] Zoha Deldar, PhD,[a] and Arantxa Ortega-De Mues, PhD[b]

ABSTRACT

Objective: The purpose of this study was to assess the effects of different spinal manipulation (SM) techniques and target segments on a specific dermatome and myotome, when compared with a remote spinal cord segment that served as a control location.

Methods: Twenty-nine healthy volunteers were randomized to receive instrumental (Activator IV, Activator Methods International Ltd) or manual SM at the C6, C1, and T4 vertebral segments in 3 independent sessions. Pressure pain thresholds (PPTs) and muscle strength were examined at the C6 (test) and L4 (control) dermatomes and myotomes, at baseline and after intervention. Linear mixed-effects models were used to analyze changes over time and interindividual variability.

Results: Pressure pain thresholds significantly increased at both proximal and distal C6 dermatome locations ($P < .05$), irrespective of the technique and segment of application ($P > .2$). No significant changes were observed at the L4 dermatome. Muscle strength remained unchanged throughout the study. Multilevel modeling revealed significant associations between increased PPTs along the C6 dermatome ($P < .001$), whereas the combination of technique and target segment predicted PPT increases at the proximal C6 dermatome.

Conclusion: These findings support regional, rather than segmental mechanisms underlying the sensory effects of SM. Specifically, significant increases in PPTs along the C6 dermatome suggest localized effects on pain sensitivity, which may depend on the target spinal region. Further investigation is needed to better understand these regional changes of SM and their potential clinical implications. (J Manipulative Physiol Ther 2024;00:1-14)

Key Indexing Terms: *Spinal Manipulation; Chiropractic; Pain Threshold; Muscle Strength*

INTRODUCTION

Spinal manipulation (SM) is a conservative manual therapy intervention that is currently recommended by multiple clinical practice guidelines for the management of spine pain.[1] Nonetheless, the specific effects of SM remain unclear.[2,3] Better understanding the specific mechanisms of SM is necessary to determine which neurophysiological changes can be attributed to the intervention, and which more likely to contextual factors.[4,5] This is essential to clarify the clinical value of SM.

There is an ongoing scientific debate concerning whether the specific parameters and segment of application of SM can alter the outcomes of the intervention.[2,6] A systematic review reported that the site of application does not influence clinical outcomes.[7] However, recent experiments support the postulate that some of the neurophysiological effects of SM are segmental in nature and thus, depend on the targeted segment.[2,8] Accordingly, it was suggested that SM may influence spinal mechanisms of pain inhibition,[9] potentially related to central sensitization.[10] More specifically, SM seems to increase pressure pain thresholds (PPTs) at the regional and/or segmental level.[11] Notwithstanding, findings consistent with a widespread effect have also been reported, particularly in patients with chronic pain.[12-14]

Regional effects of SM on pain sensitivity have also been measured on myotomal tissues related to the targeted segment,[15,16] indicating that SM may impact segmental muscle function. Accordingly, recent reviews suggested

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Review

Pain-sensorimotor interactions: New perspectives and a new model

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Electromyography

ABSTRACT

How pain and sensorimotor behavior interact has been the subject of research and debate for many decades. This article reviews theories bearing on pain-sensorimotor interactions and considers their strengths and limitations in the light of findings from experimental and clinical studies of pain-sensorimotor interactions in the spinal and craniofacial sensorimotor systems. A strength of recent theories is that they have incorporated concepts and features missing from earlier theories to account for the role of the sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions of pain in pain-sensorimotor interactions. Findings acquired since the formulation of these recent theories indicate that additional features need to be considered to provide a more comprehensive conceptualization of pain-sensorimotor interactions. These features include biopsychosocial influences that range from biological factors such as genetics and epigenetics to psychological factors and social factors encompassing environmental and cultural influences. Also needing consideration is a mechanistic framework that includes other biological factors reflecting nociceptive processes and gliopathic and neuropathic changes in sensorimotor and related brain and spinal cord circuits in acute or chronic pain conditions. The literature reviewed and the limitations of previous theories bearing on pain-sensorimotor interactions have led us to provide new perspectives on these interactions, and this has prompted our development of a new concept, the Theory of Pain-Sensorimotor Interactions (TOPSMI) that we suggest gives a more comprehensive framework to consider the interactions and their complexity. This theory states that ***pain is associated with plastic changes in the central nervous system (CNS) that lead to an activation pattern of motor units that contributes to the individual's adaptive sensorimotor behavior. This activation pattern takes account of the biological, psychological, and social influences on the musculoskeletal tissues involved in sensorimotor behavior and on the plastic changes and the experience of pain in that individual. The pattern is normally optimized in terms of biomechanical advantage and metabolic cost related to the features of the individual's musculoskeletal tissues and aims to minimize pain and any associated sensorimotor changes, and thereby maintain homeostasis. However, adverse biopsychosocial factors and their interactions may result in plastic CNS changes leading to less optimal, even maladaptive, sensorimotor changes producing motor unit activation patterns associated with the development of further pain.*** This more comprehensive theory points towards customized treatment strategies, in line with the management approaches to pain proposed in the biopsychosocial model of pain.

1. Introduction

Pain is a complex multi-dimensional experience reflecting sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions (Fulbert et al., 1978; Fillingim, 2017; Kuner and Flor, 2017; De Silva and Seminowicz, 2019; Kuner and Kuner, 2021; Sessle, 2021). The sensory-discriminative dimension reflects such aspects as the location and intensity of pain that are commonly described by humans experiencing pain, in particular acute pain which is a transient form of pain that is typically associated with a clearly identifiable noxious stimulus. This dimension relies heavily on nociceptive transmission and processing along ascending nociceptive pathways within the central nervous system (CNS), although these processes themselves can be modulated by projections from CNS areas involved in the various dimensions of pain (Kuner and Flor, 2017; De Silva and Seminowicz, 2019; Kuner and Kuner, 2021). The motivational-affective and cognitive-

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Magnificent Insight from Harvard and our DCs...

American Pain Society — RESEARCH EDUCATION TREATMENT ADVOCACY

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Available online at www.jpain.org and www.sciencedirect.com

Brain Mechanisms of Anticipated Painful Movements and Their Modulation by Manual Therapy in Chronic Low Back Pain

Dan-Mikael Ellingsen,* Vitaly Napadow,* Ekaterina Protsenko,*,† Ishtiaq Mawla,*,‡ Matthew H. Kowalski,§ David Swensen,¶ Deanna O'Dwyer-Swensen,¶ Robert R. Edwards,‖ Norman Kettner,** and Marco L. Loggia*

*A. A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, †School of Medicine, University of California, San Francisco, California, ‡Neuroscience Graduate Program, University of Michigan Medical School, Ann Arbor Michigan, §Osher Integrative Care Center, Brigham and Women's Hospital, Boston, MA, Massachusetts, ¶Melrose Family Chiropractic & Sports Injury Centre, Melrose, Massachusetts, ‖Department of Anesthesiology, Harvard Medical School, Brigham & Women's Hospital, Boston, Massachusetts, **Department of Radiology, Logan University, Chesterfield, Missouri

In cLBP patients, **SMT reduced both clinical pain and aversiveness** (fear and expected pain).

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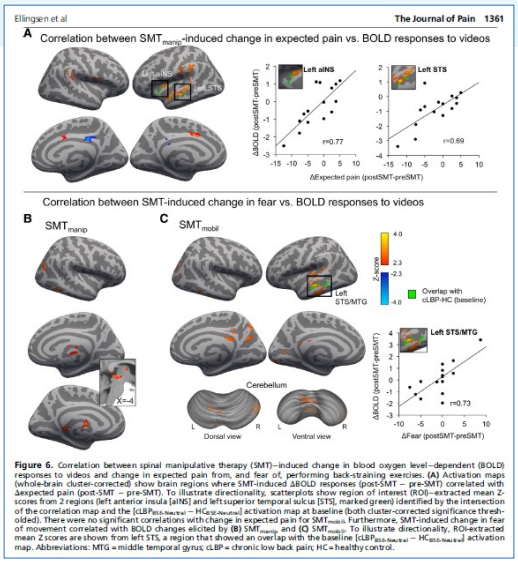

Figure 6. Correlation between spinal manipulative therapy (SMT)–induced change in blood oxygen level–dependent (BOLD) responses to videos and change in expected pain from, and fear of, performing back-straining exercises. **(A)** Activation maps (whole-brain cluster-corrected) show brain regions where SMT-induced ΔBOLD responses (post-SMT – pre-SMT) correlated with Δexpected pain (post-SMT – pre-SMT). To illustrate directionality, scatterplots show region of interest (ROI)–extracted mean Z-scores from 2 regions (left anterior insula [aINS] and left superior temporal sulcus [STS], marked green) identified by the intersection of the correlation map and the [cLBP$_{BOLD-Task/Trial}$ – HC$_{BOLD-Narrative}$] activation map at baseline (both cluster-corrected significance threshholded). There were no significant correlations with change in expected pain for SMT$_{mobil}$. Furthermore, SMT-induced change in fear of movement correlated with BOLD changes elicited by **(B)** SMT$_{manip}$ and **(C)** SMT$_{mobil}$. To illustrate directionality, ROI-extracted mean Z scores are shown from left STS, a region that showed an overlap with the baseline [cLBP$_{BOLD-Task/Trial}$ – HC$_{BOLD-Task/Trial}$] activation map. Abbreviations: MTG = middle temporal gyrus; cLBP = chronic low back pain; HC = healthy control.

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Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Increased Salience Network Connectivity Following Manual Therapy is Associated with Reduced Pain in Chronic Low Back Pain Patients

Kylie Isenburg,* Ishtiaq Mawla,* Marco L. Loggia,* Dan-Mikael Ellingsen,* Ekaterina Protsenko,* Matthew H. Kowalski,† David Swensen,‡ Deanna O'Dwyer-Swensen,‡ Robert R. Edwards,§ Vitaly Napadow,*,§,‖ and Norman Kettner‖

*Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts, †Osher Center for Complementary and Integrative Medical Therapies, Brigham & Women's Hospital, Boston, Massachusetts, ‡Melrose Family Chiropractic & Sports Injury Centre, Melrose, Massachusetts, §Department of Anesthesiology, Harvard Medical School, Brigham & Women's Hospital, Boston, Massachusetts, ‖Department of Radiology, Logan University, Chesterfield, Missouri

Perspective: ***MT both reduces clinical low back pain and modulates brain activity important for the processing of pain. This modulation was shown by increased functional brain connectivity between the salience network and brain regions involved in cognitive, affective, and sensorimotor processing of pain.***

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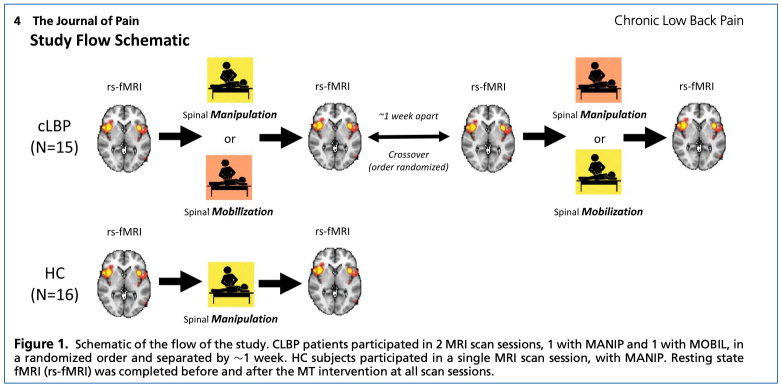

Figure 1. Schematic of the flow of the study. CLBP patients participated in 2 MRI scan sessions, 1 with MANIP and 1 with MOBIL, in a randomized order and separated by ~1 week. HC subjects participated in a single MRI scan session, with MANIP. Resting state fMRI (rs-fMRI) was completed before and after the MT intervention at all scan sessions.

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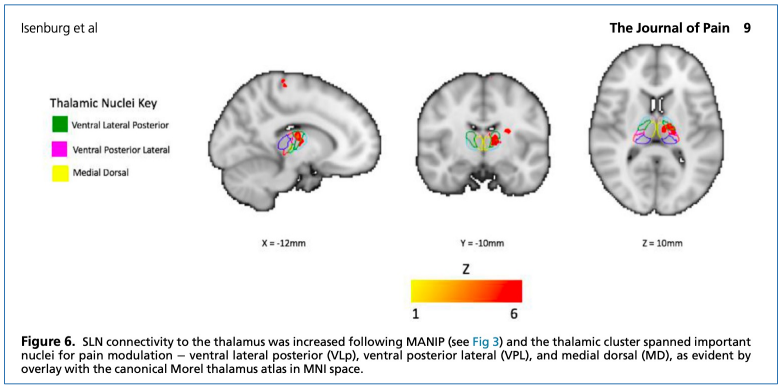

Figure 6. SLN connectivity to the thalamus was increased following MANIP (see Fig 3) and the thalamic cluster spanned important nuclei for pain modulation – ventral lateral posterior (VLp), ventral posterior lateral (VPL), and medial dorsal (MD), as evident by overlay with the canonical Morel thalamus atlas in MNI space.

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frontiers in Pain Research

MINI REVIEW

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Brainstem Diffusion Tensor Tractography and Clinical Applications in Pain

Yu Zhang† and Ansgar J. Furst†‡§¶*

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The brainstem is one of the most vulnerable brain structures in many neurological conditions, such as pain, sleep problems, autonomic dysfunctions, and neurodegenerative disorders. Diffusion tensor imaging and tractography provide structural details and quantitative measures of brainstem fiber pathways. Until recently, diffusion tensor tractographic studies have mainly focused on whole-brain MRI acquisition. Due to the brainstem's spatial localization, size, and tissue characteristics, and limits of imaging techniques, brainstem diffusion MRI poses particular challenges in tractography. We provide a brief overview on recent advances in diffusion tensor tractography in revealing human pathways connecting the brainstem to the subcortical regions (e.g., basal ganglia, mesolimbic, basal forebrain), and cortical regions. Each of these pathways contains different distributions of fiber tracts from known neurotransmitter-specific nuclei in the brainstem. We compare the brainstem tractographic approaches in literature and our in-lab developed automated brainstem tractography in terms of atlas building, technical advantages, and neuroanatomical implications on neurotransmitter systems. Lastly, we summarize recent investigations of using brainstem tractography as a promising tool in association with pain.

Keywords: diffusion tensor imaging, diffusion tensor tractography, brainstem, pain, descending pain modulation

OPEN ACCESS

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INTRODUCTION

The brainstem is a central structure that connects the brain cerebrum to the spinal cord and cerebellum. The brainstem contains nuclei and fiber pathways that synthesize and transfer specific neurotransmitters and neuromodulators to the peripheral receptors and effectors for the regulation of such basic functions as arousal, motor function, memory, reward, nociception, and autonomic control. Along a dorsoventral axis, the brainstem consists of three subdivisions with distinctive parts: the dorsal side of the midbrain known as the tectum, including the mid-dorsal part of the aqueduct, a central region of nuclei and fibers known as tegmentum beneath the ventricular system, and a massive fiber communication system connecting to the spinal cord and the cerebellum in the ventral part. Nuclei and fiber pathways in the tectum relay pain signals from peripheral stimuli via the spinal cord to the cerebral sensory cortices that result in the sensation of pain (nociception). They also transmit anti-nociceptive signals down to the spinal cord which induces endogenous opioid-based analgesia (pain regulation). Many pain syndromes can be caused by damage to or

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- The brainstem is one of the most vulnerable brain structures in many neurological conditions, such as pain, sleep problems, autonomic dysfunctions, and neurodegenerative disorders.
- Diffusion tensor imaging and tractography provide structural details and quantitative measures of brainstem fiber pathways.

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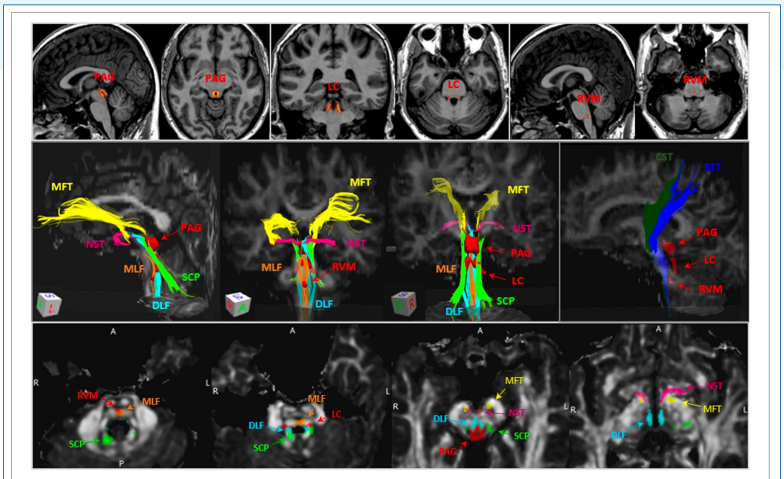

FIGURE 3 | Illustration of ROI where the volumes of the brainstem nuclei and diffusion metrics were measured. *Upper panel*, Illustration of ROIs of the PAG, LC and RVM, which were delineated based on literature (108). The hot color scale represents probability of gray matter density (brighter color refers to higher gray matter density) within the ROIs. *Middle panel*, example of brainstem tracts of interests, including MLF (orange), DLF (cyan), SCP (green), NST (dark pink), MFT (yellow), CST (dark green), STT (blue), and the three brainstem nuclei (red). *Lower panel*, the anatomical relationships between brainstem tracts (non-red) and nuclei (red) on 4 brainstem axial slices. PAG, periaqueductal gray; LC, locus coeruleus; RVM, rostral ventromedial medulla; MLF, medial longitudinal fasciculus; DLF, dorsal longitudinal fasciculus; SCP, superior cerebellar peduncle; NST, nigrostriatal tract; MFT, medial forebrain tract; CST, corticospinal tract; STT, spinothalamic tract.

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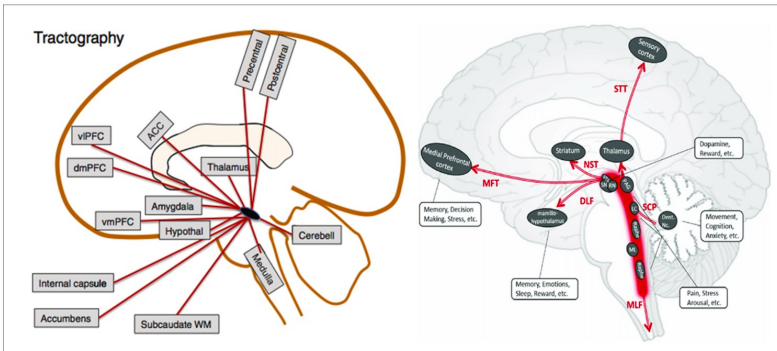

FIGURE 2 | Possible PAG connections based on DTI from Linnman et al. (84) and Zhang et al. (76). ACC, anterior cingulate cortex; Cerebell, cerebellum; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; WM, white matter; VTA, ventral tegmental area; SN, substantia nigra; RN, red nucleus; PAG, periaqueductal gray matter; LC, locus coeruleus; ML, medial lemniscus; Dent. Nc., dentate nucleus; STT, spinothalamic tract; NST, nigrostriatal tract; MFT, medial forebrain tract; DLF, dorsal longitudinal fasciculus; SCP, superior cerebellar peduncle; MLF, medial longitudinal fasciculus.

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Moderated by: **James Demetrious, DC, DABCO**

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David Seaman, DC, DACNB

Instructor: David Seaman, MS, DC, DACNB

Dr. Seaman is a graduate of NYCC. He is a Diplomate of the American Board of Chiropractic Neurologists & American College of Chiropractic Neurology. He has written many articles and books on the topic of pain, inflammation, diet, and obesity management.

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Seaman *Chiropractic & Manual Therapies* 2013, **21**:15
http://www.chiromt.com/content/21/1/15

CHIROPRACTIC & MANUAL THERAPIES

COMMENTARY Open Access

Body mass index and musculoskeletal pain: is there a connection?

David R Seaman

Abstract

Background: Back pain is one of the most common complaints that patients report to physicians and two-thirds of the population has an elevated body mass index (BMI), indicating they are either overweight or obese. It was once assumed that extra body weight would stress the low back and lead to pain, however, researchers have reported inconsistencies association between body weight and back pain. In contrast, more recent studies do indicate that an elevated BMI is associated with back pain and other musculoskeletal pain syndromes due to the presence of a chronic systemic inflammatory state, suggesting that the relationship between BMI and musculoskeletal pains be considered in more detail.

Objective: To describe how an elevated BMI can be associated with chronic systemic inflammation and pain expression. To outline measurable risk factors for chronic inflammation that can be used in clinical practice and discuss basic treatment considerations.

Discussion: Adiposopathy, or "sick fat" syndrome, is a term that refers to an elevated BMI that is associated with a chronic systemic inflammatory state most commonly referred to as the metabolic syndrome. The best available evidence suggests that the presence of adiposopathy determines if an elevated BMI will contribute to musculoskeletal pain expression. It is not uncommon for physicians to fail to identify the presence of adiposopathy/

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Table 1 Markers of chronic inflammation

Markers		Date	Date	Date	Date
Metabolic syndrome	**Abnormal value**				
1. Fasting blood glucose	≥ 100 mg/dL				
2. Triglycerides	≥ 150 mg/dL				
3. HDL cholesterol	< 50 for women; < 40 men				
4. Blood pressure	≥ 130/85				
5. Waist circumference	> 35" women; > 40" men				
Pro-inflammatory markers	**Parameters**				
2-hour postprandial glucose	<140 mg/dl = normal				
	140–199 = prediabetes				
	200+ = diabetes				
Fasting triglycerides	<90 mg/dl predicts controlled postprandial response				
hsCRP in mg/L (marker of chronic inflammation)	<1.0 = normal				
	1.0-3.0 = moderate				
	>3.0 = high				
25(OH)D (vitamin D)	32-100 ng/ml (goal >40 ng)				
Body mass index (BMI)	18.5-24.9 = normal Text				
	25–29.9 = overweight				
	≥30 = obese				
Waist/hip ratio women (risk factor for diabetes)	<0.80 = low risk				
	0.81-.85 = moderate risk				
	>0.85 = high risk				
Waist/hip ratio men (risk factor for diabetes)	<0.95 = low risk				
	0.96-1.0 = moderate risk				
	>1.0 = high risk				
Lack of sleep	Less than 6 hrs				
Stress	Associated with systemic inflammation				
Sedentary living	Associated with systemic inflammation				
Depression	Associated with systemic inflammation				
Self-rated health	Associated with systemic inflammation				

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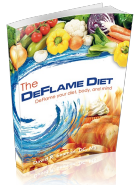
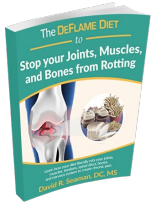
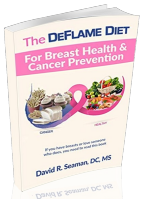
Table 3 - Metabolic syndrome markers

Metabolic syndrome	Abnormal value	Date	Date	Date	Date
1. Fasting blood glucose	≥ 100 mg/dL				
2. Fasting triglycerides	≥ 150 mg/dL				
3. Fasting HDL cholesterol	< 50 for women; < 40 men				
4. Blood pressure	≥ 130/85				
5. Waist circumference	> 35" women; > 40" men				







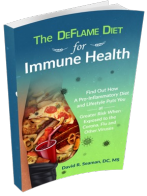


Table 4 - General markers of inflammation

Pro-inflammatory markers	Parameters	Date	Date	Date	Date
Fasting glucose	65-80 mg/dl = ketogenic diet 80-90 = low carbohydrate diet < 100 = considered normal 100-125 = pre-diabetes >125 = type 2 diabetes				
2-hour postprandial glucose	<140 mg/dl = normal 140-199 = pre-diabetes 200+ = diabetes				
Hemoglobin A1c (HbA1c)	<5.7% = normal 5.7-6.4% = pre-diabetes ≥6.5% = type 2 diabetes				
Fasting triglycerides	<90 mg/dl predicts controlled postprandial response				
Fasting triglyceride/HDL ratio	>3.5 = oxidation of LDL cholesterol				
Blood pressure goal	Less than 120/80 = normal 120-139/80-89 = pre-hypertension 140-159/90-99 = Stage 1 hypertension ≥160/100 = Stage 2 hypertension				
Waist circumference goal - men	33" or less				
Waist circumference goal - women	28" or less				
Women waist/hip ratio (risk factor for type 2 diabetes = inflammation)	<0.80 = normal 0.81-.85 = moderate inflammation >0.85 = high inflammation				
Men waist/hip ratio (risk factor for type 2 diabetes = inflammation)	<0.95 = normal 0.96-1.0 = moderate inflammation >1.0 = high inflammation				
Body mass index (BMI)	18.5-24.9 = normal 25-29.9 = overweight ≥30 = obese				
hsCRP in mg/L (general marker of chronic inflammation)	<1.0 = normal 1.0-3.0 = moderate inflammation >3.0 = high inflammation				
25(OH)D (vitamin D)	32-100 ng/ml (goal at least 60-80ng)				

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Natural management of Msk Pain

Natural management of all painful spinal conditions are based on the patients response to care – it is impossible to predict in advance, which treatment will best serve the patient. Treatment options for IDDs and other painful spinal conditions:

- **Manual care**
  - HVLA manipulation
  - Distraction
  - End range loading
  - Soft tissue mobilization
  - Nerve mobilization
- **Exercise**
  - Stabilization
  - Cardiovascular
  - Sensory-motor
- **Psychosocial**
  - Education
  - Reassurance
  - Referral
- **Anti-inflammatory nutrition**
  - Diet
  - Supplements

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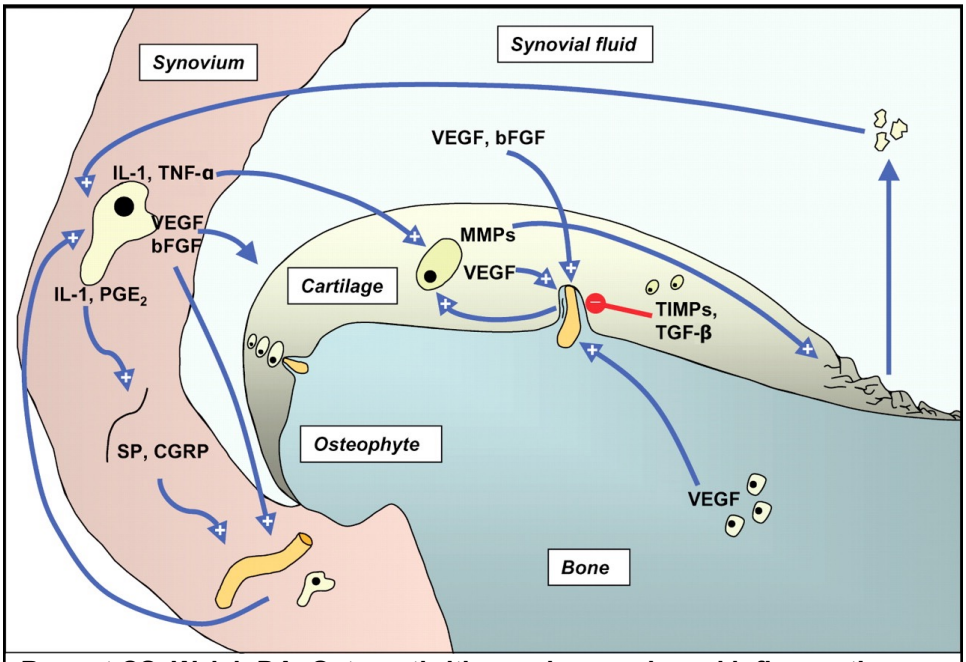

Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford). 2005 Jan;44(1):7-16

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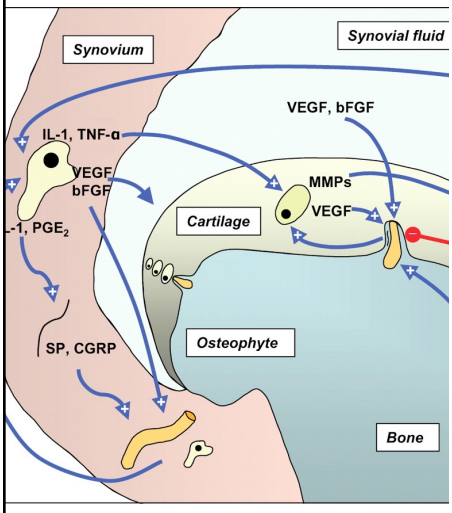

TABLE 1. Angiogenesis regulators localized to or released within oste

Stimulators	
Synovial fluid/synovium	Articular chondrocyte
Bradykinin*	SP [36]
SP*	PGE_2 [37]
CGRP*	Nitric oxide [38]
Angiotensin II*	Histamine [39]
PGE_2*	$VEGF_{121/189}$ [15]
Nitric oxide*	Endoglin [40]
Histamine*	Hepatocyte growth factor [41]
$VEGF_{121/189}$ [15]*	IL-1 [42]
Angiopoietin-1 [16]*	IL-8 [43]
bFGF*	$TGF\text{-}\beta_{1/2/3}$ [44]
Endoglin*	TNF-α [45]
Hepatocyte growth factor*	IL-18 [46]
Epidermal growth factor*	Connective tissue grow factor [47, 48]
IL-1 [17]*	
IL-8 [18]*	
Angiogenin*	
TGF-β [19]*	
TNF-α [20]*	
Platelet-derived endothelial cell growth factor*	
Endothelial cell-stimulating angiogenesis factor*	
Hyaluronic acid (low molecular weight)*	
IL-18 [21, 22]	
Stem cell-derived factor-1 [23, 24]	
Fractalkine [25, 26]	
Platelet-derived growth factor [27, 28]	
Pleiotrophin [29, 30]	
Soluble E-selectin [31, 32]	
Vascular cell adhesion molecule-1 [31, 33]	
IL-4 [34, 35]	

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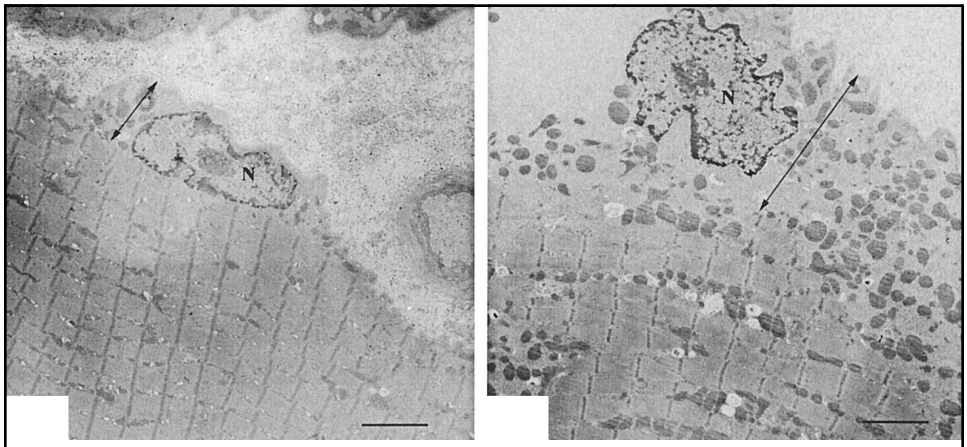
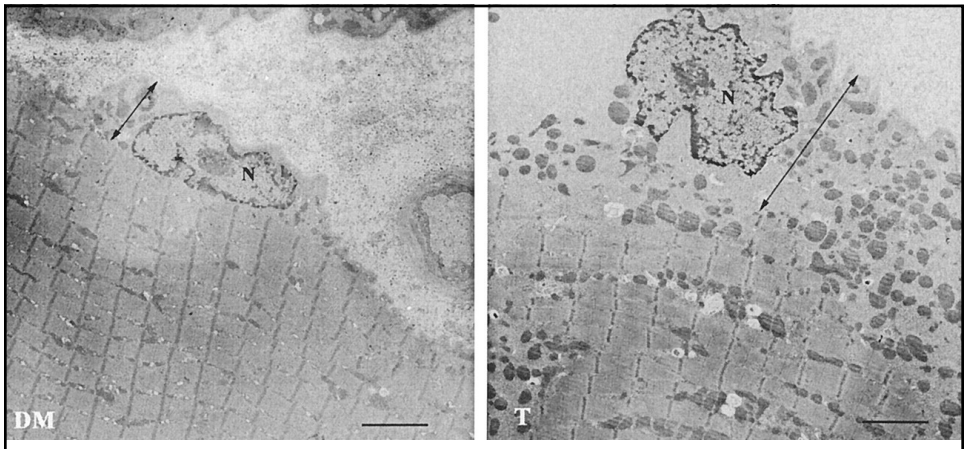


Electron micrograph of skeletal muscle.

Which one is normal??

26



Representative transmission electron microscopy of longitudinal sections of human skeletal muscle from a lean (T) and a type 2 diabetic (DM) research volunteer are shown (bar = 2.5 μm). The thickness of the perinuclear distribution of subsarcolemmal mitochondria was measured using image analysis (National Institutes of Health image 1.61) and can be observed to be substantially depleted in type 2 diabetes.

Ritov VB et al. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. Diabetes 2005; 54(1):8-14.

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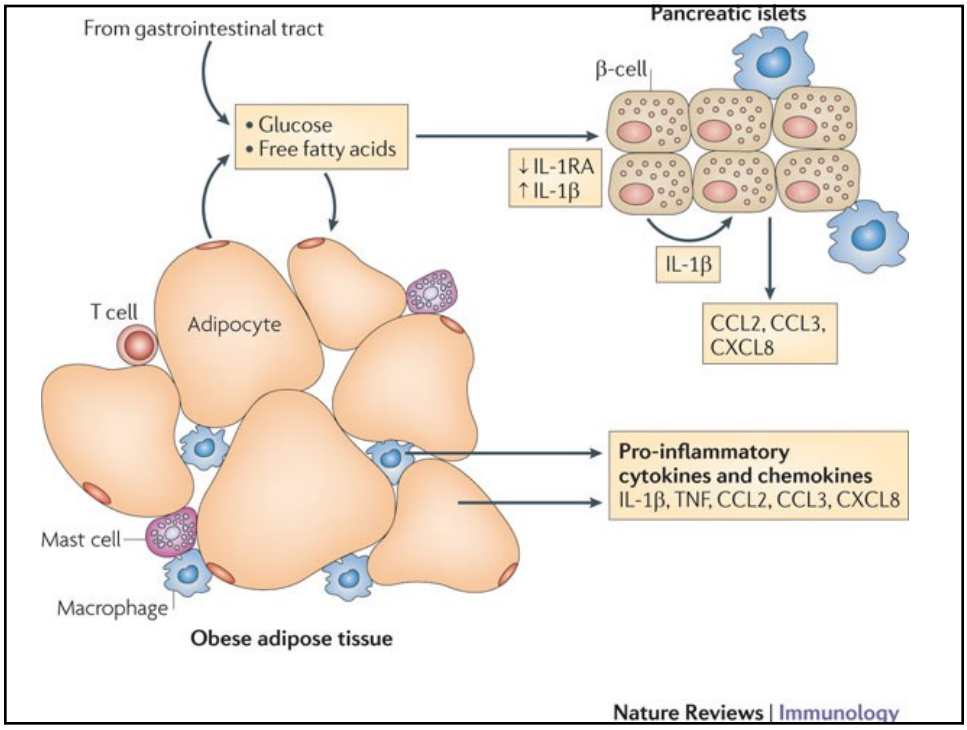
28



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458 Journal of Manipulative and Physiological Therapeutics
Volume 22 • Number 7 • September 1999
0161-4754/99/$8.00 + 0 **76/1/100399** © 1999 JMPT

REVIEW OF THE LITERATURE

Spinal Pain Syndromes: Nociceptive, Neuropathic, and Psychologic Mechanisms

David R. Seaman, DC, MS,[a] and Carl Cleveland III, DC[b]

ABSTRACT

Background: Pain continues to be the main symptom reported by patients. Frequently, clinicians incorrectly diagnose patients and resulting treatments are ineffective, which may promote the development of chronic pain. This situation may arise as a result of a lack of clarity in the literature regarding pain syndromes.

Objective: To discuss the differences between nociceptive, neuropathic, and psychologic induction of pain and provide important clinical correlates to aid in diagnosis and treatment.

Data Sources: The data were accumulated over a period of years by reviewing contemporary articles and books and subsequently retrieving relevant papers. Articles also were selected from MEDLINE searches and from manual library searches.

Data Synthesis: Nociceptive pain syndromes are responsible for the majority of pain complaints in clinical practice. Care must be taken to avoid the common mistake of the diagnosis of neuropathic pain, which can lead to inappropriate treatments.

Conclusions: Although the treatment of neuropathic pain is difficult, sufficient evidence in the literature demonstrates that the treatment of nociceptive pain should be multimodal and involve spinal manipulation, muscle lengthening/stretching, trigger point therapy, rehabilitation exercises, electrical modalities, a variety of nutritional factors, and mental/emotional support. (J Manipulative Physiol Ther 1999;22:458-72)

Key Indexing Terms: Pain; Referred Pain; Nociception; Joints

INTRODUCTION

The subject of pain has always been a focus of attention graine, temporomandibular joint syndrome, trigeminal neuralgia, the majority of neck and back pains, fi-

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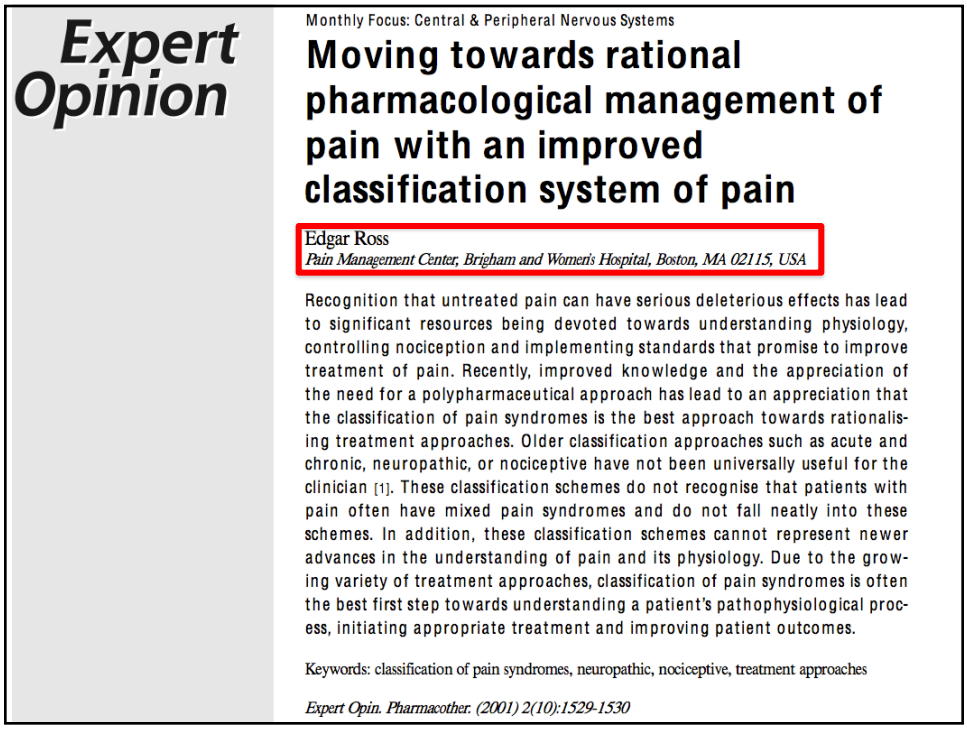


Expert Opinion

Monthly Focus: Central & Peripheral Nervous Systems

Moving towards rational pharmacological management of pain with an improved classification system of pain

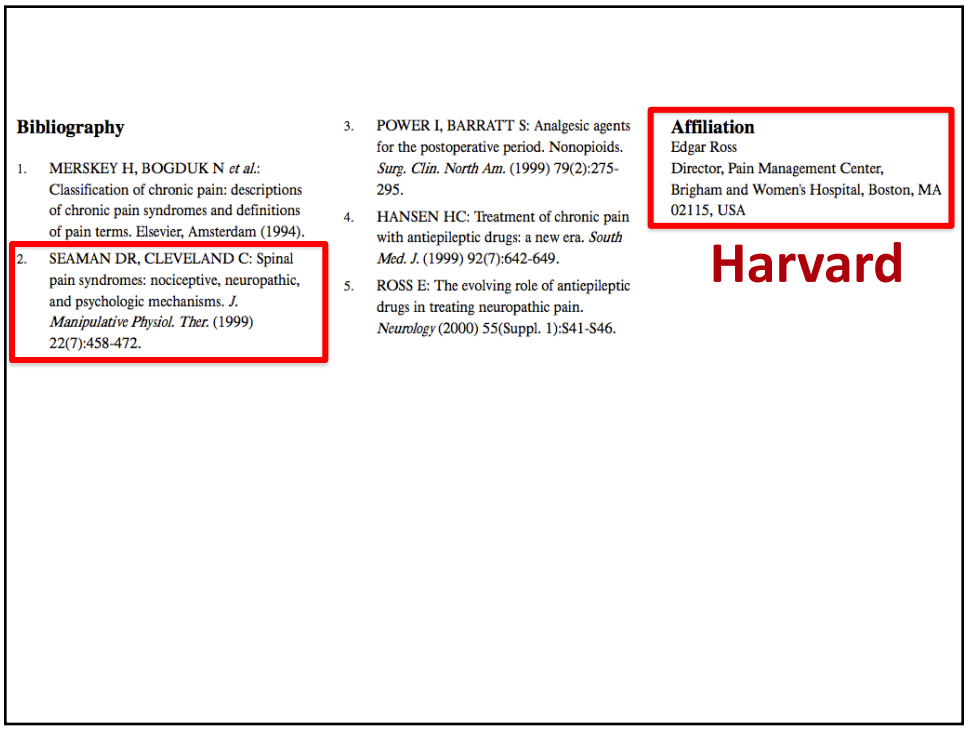
Edgar Ross
Pain Management Center, Brigham and Women's Hospital, Boston, MA 02115, USA

Recognition that untreated pain can have serious deleterious effects has lead to significant resources being devoted towards understanding physiology, controlling nociception and implementing standards that promise to improve treatment of pain. Recently, improved knowledge and the appreciation of the need for a polypharmaceutical approach has lead to an appreciation that the classification of pain syndromes is the best approach towards rationalising treatment approaches. Older classification approaches such as acute and chronic, neuropathic, or nociceptive have not been universally useful for the clinician [1]. These classification schemes do not recognise that patients with pain often have mixed pain syndromes and do not fall neatly into these schemes. In addition, these classification schemes cannot represent newer advances in the understanding of pain and its physiology. Due to the growing variety of treatment approaches, classification of pain syndromes is often the best first step towards understanding a patient's pathophysiological process, initiating appropriate treatment and improving patient outcomes.

Keywords: classification of pain syndromes, neuropathic, nociceptive, treatment approaches

Expert Opin. Pharmacother. (2001) 2(10):1529-1530

31



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2. SEAMAN DR, CLEVELAND C: Spinal pain syndromes: nociceptive, neuropathic, and psychologic mechanisms. *J. Manipulative Physiol. Ther.* (1999) 22(7):458-472.
3. POWER I, BARRATT S: Analgesic agents for the postoperative period. Nonopioids. *Surg. Clin. North Am.* (1999) 79(2):275-295.
4. HANSEN HC: Treatment of chronic pain with antiepileptic drugs: a new era. *South Med. J.* (1999) 92(7):642-649.
5. ROSS E: The evolving role of antiepileptic drugs in treating neuropathic pain. *Neurology* (2000) 55(Suppl. 1):S41-S46.

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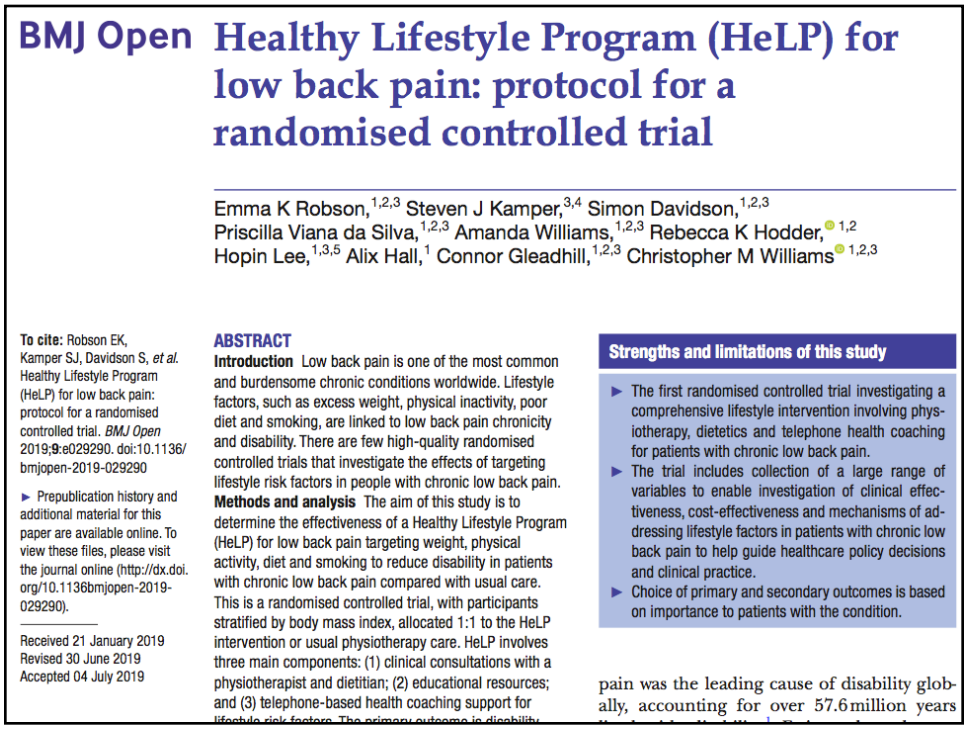

BMJ Open

Healthy Lifestyle Program (HeLP) for low back pain: protocol for a randomised controlled trial

Emma K Robson,[1,2,3] Steven J Kamper,[3,4] Simon Davidson,[1,2,3] Priscilla Viana da Silva,[1,2,3] Amanda Williams,[1,2,3] Rebecca K Hodder,[1,2] Hopin Lee,[1,3,5] Alix Hall,[1] Connor Gleadhill,[1,2,3] Christopher M Williams[1,2,3]

To cite: Robson EK, Kamper SJ, Davidson S, *et al*. Healthy Lifestyle Program (HeLP) for low back pain: protocol for a randomised controlled trial. *BMJ Open* 2019;**9**:e029290. doi:10.1136/bmjopen-2019-029290

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136bmjopen-2019-029290).

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Revised 30 June 2019
Accepted 04 July 2019

ABSTRACT

Introduction Low back pain is one of the most common and burdensome chronic conditions worldwide. Lifestyle factors, such as excess weight, physical inactivity, poor diet and smoking, are linked to low back pain chronicity and disability. There are few high-quality randomised controlled trials that investigate the effects of targeting lifestyle risk factors in people with chronic low back pain.

Methods and analysis The aim of this study is to determine the effectiveness of a Healthy Lifestyle Program (HeLP) for low back pain targeting weight, physical activity, diet and smoking to reduce disability in patients with chronic low back pain compared with usual care. This is a randomised controlled trial, with participants stratified by body mass index, allocated 1:1 to the HeLP intervention or usual physiotherapy care. HeLP involves three main components: (1) clinical consultations with a physiotherapist and dietitian; (2) educational resources; and (3) telephone-based health coaching support for lifestyle risk factors. The primary outcome is disability

Strengths and limitations of this study

- ► The first randomised controlled trial investigating a comprehensive lifestyle intervention involving physiotherapy, dietetics and telephone health coaching for patients with chronic low back pain.
- ► The trial includes collection of a large range of variables to enable investigation of clinical effectiveness, cost-effectiveness and mechanisms of addressing lifestyle factors in patients with chronic low back pain to help guide healthcare policy decisions and clinical practice.
- ► Choice of primary and secondary outcomes is based on importance to patients with the condition.

pain was the leading cause of disability globally, accounting for over 57.6 million years

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Physical inactivity and poor diet contribute to obesity, and have an influence on chronic low back pain independently.[13–18] Despite some inconsistency in the literature, evidence suggests low levels of physical activity are associated with chronic low back pain,[13–15] as is diet-induced systematic inflammation.[16 17]

16. Seaman DR. The diet-induced proinflammatory state. J Manipulative Physiol Ther 2002;25:168–79. 10.1067/mmt.2002.122324 [DOI] [PubMed] [Google Scholar]

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Pain syndrome classification

- **Nociceptive pain**
- **Ectopic nociceptive pain**
  [that transiently presents as neuropathic-like pain but resolves/improves as nociceptive]
- **Neuropathic pain**
- **Psychogenic pain (psychologic)**

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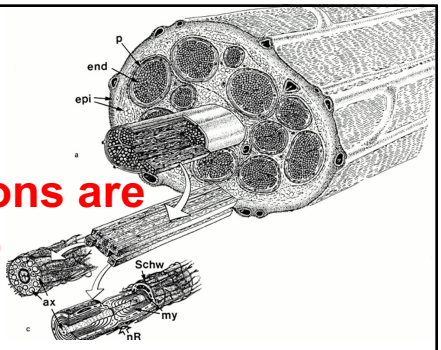


Neuropathic pain: if axons are damaged and unable to heal

Nociceptive pain: if epineurium is inflamed and group IVs are activated

Ectopic nociceptive pain: if axons are inflamed

Can have all 3 present

36

Diagnostic categories of pain

- Mechanical pain
- Radiating leg pain
- Cancer pain
- Pain due to infection
- Rheumatological pain
- Visceral pain
- Inflammatory pain

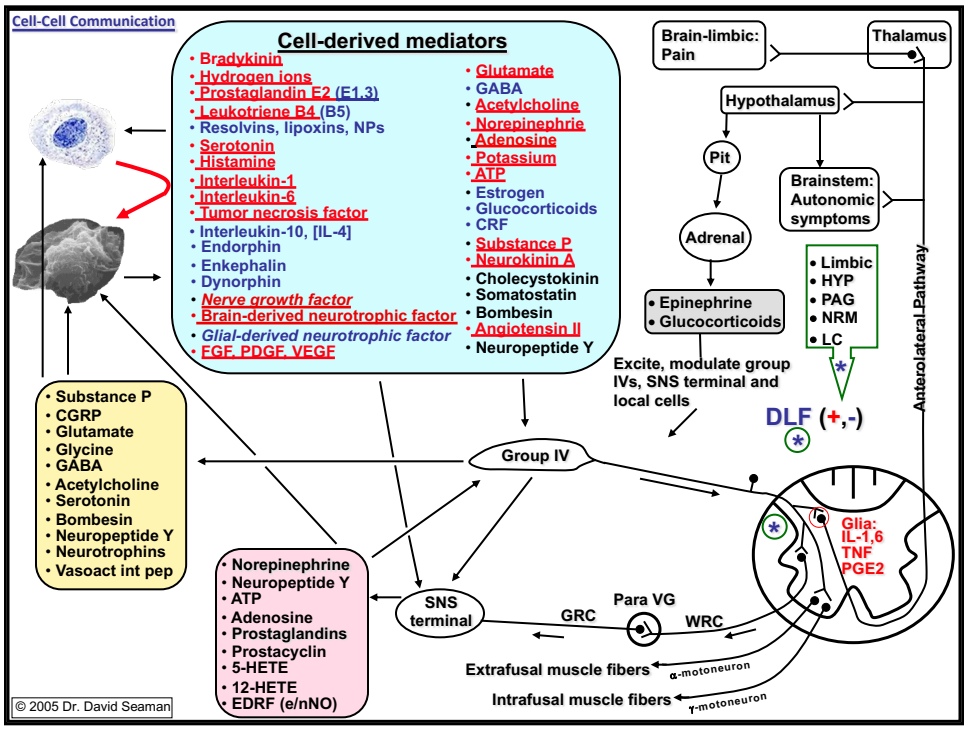
Mechanism of pain generation:

Nociceptive pain (caused by stim of group IVs)

Ectopic nociceptive pain (caused by inflamed axons)

Neuropathic pain (caused by damaged unhealed NS)

37



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Published in final edited form as:
Int Anesthesiol Clin. 2007 ; 45(2): 27–37. doi:10.1097/AIA.0b013e318034194e.

Cytokines, Inflammation and Pain

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[2]Department of Anesthesiology and Pain Medicine, Tsinghua University Yuquan Hospital, #5 ShiJingShan Road, Beijing, 100049, China

Abstract

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons. Certain inflammatory cytokines are also involved in nerve-injury/inflammation-induced central sensitization, and are related to the development of contralateral hyperalgesia/allodynia. The discussion presented in this chapter describes several key pro-inflammatory cytokines/chemokines and anti-inflammatory cytokines, their relation with pathological pain in animals and human patients, and possible underlying mechanisms.

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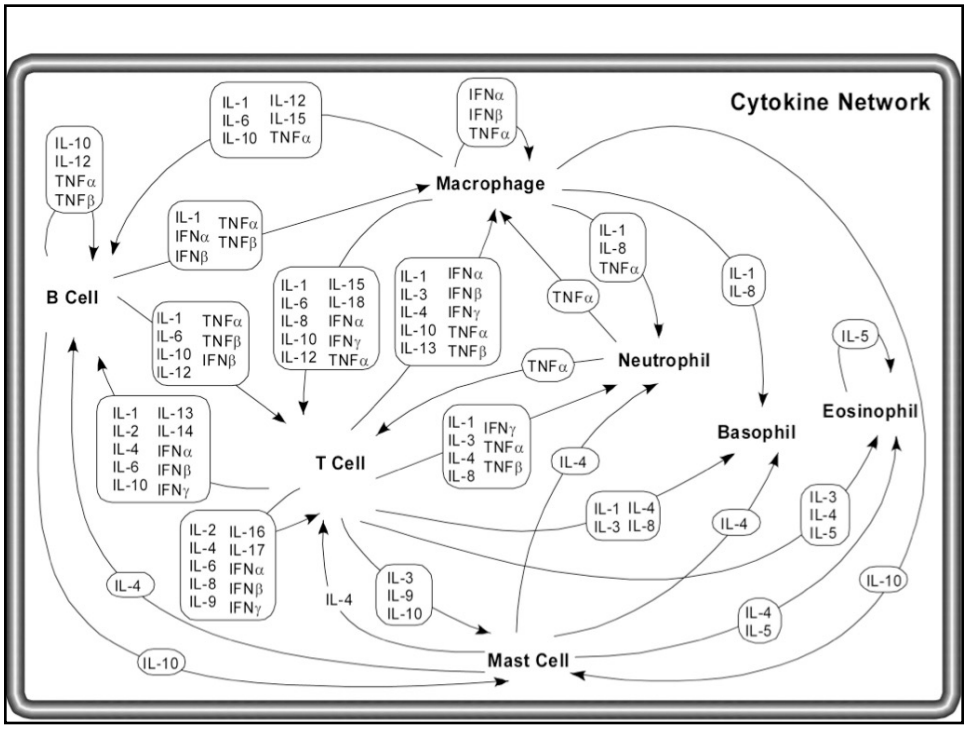

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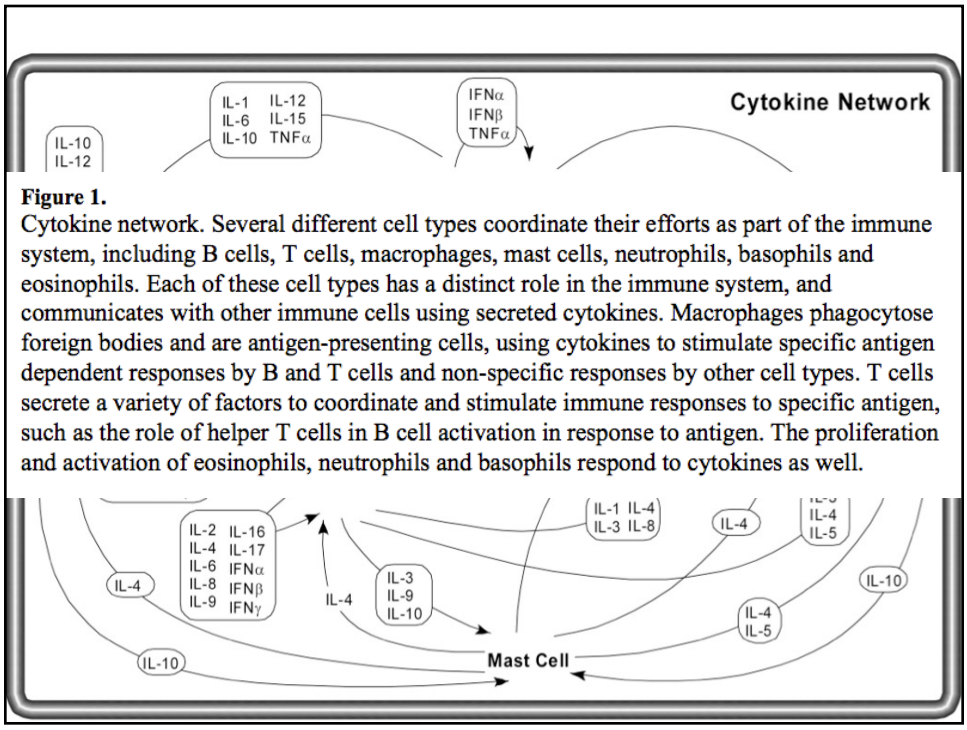

Figure 1.
Cytokine network. Several different cell types coordinate their efforts as part of the immune system, including B cells, T cells, macrophages, mast cells, neutrophils, basophils and eosinophils. Each of these cell types has a distinct role in the immune system, and communicates with other immune cells using secreted cytokines. Macrophages phagocytose foreign bodies and are antigen-presenting cells, using cytokines to stimulate specific antigen dependent responses by B and T cells and non-specific responses by other cell types. T cells secrete a variety of factors to coordinate and stimulate immune responses to specific antigen, such as the role of helper T cells in B cell activation in response to antigen. The proliferation and activation of eosinophils, neutrophils and basophils respond to cytokines as well.

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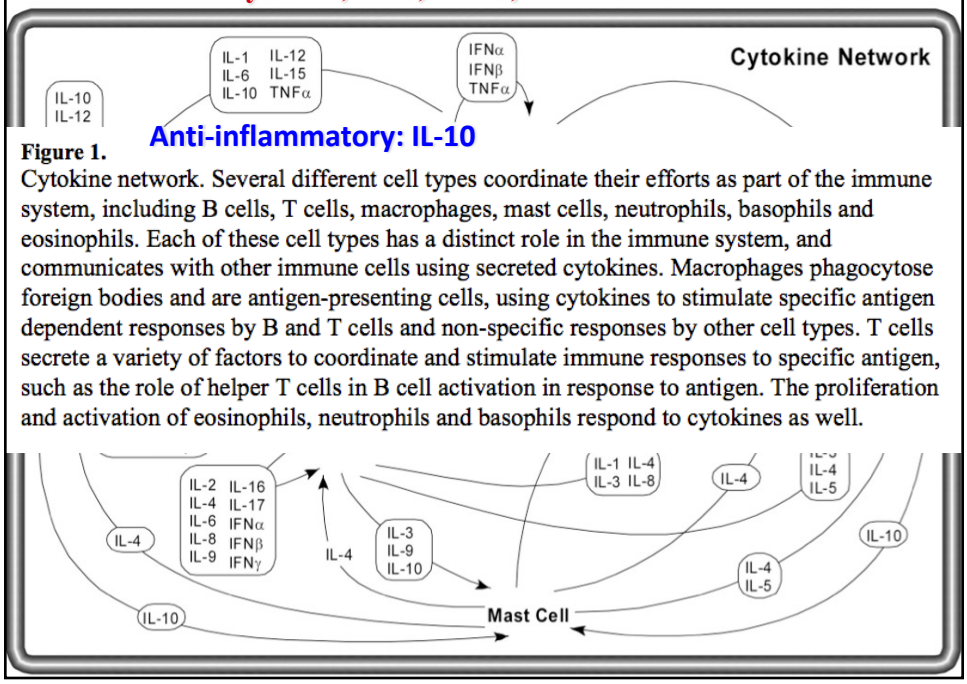
Pro-inflammatory: IL-1, IL-6, IL-17, TNF



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Cytokine network. Several different cell types coordinate their efforts as part of the immune system, including B cells, T cells, macrophages, mast cells, neutrophils, basophils and eosinophils. Each of these cell types has a distinct role in the immune system, and communicates with other immune cells using secreted cytokines. Macrophages phagocytose foreign bodies and are antigen-presenting cells, using cytokines to stimulate specific antigen dependent responses by B and T cells and non-specific responses by other cell types. T cells secrete a variety of factors to coordinate and stimulate immune responses to specific antigen, such as the role of helper T cells in B cell activation in response to antigen. The proliferation and activation of eosinophils, neutrophils and basophils respond to cytokines as well.

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The role of inflammation in depression: from evolutionary imperative to modern treatment target

Andrew H. Miller[1] and Charles L. Raison[2]

Abstract | Crosstalk between inflammatory pathways and neurocircuits in the brain can lead to behavioural responses, such as avoidance and alarm, that are likely to have provided early humans with an evolutionary advantage in their interactions with pathogens and predators. However, in modern times, such interactions between inflammation and the brain appear to drive the development of depression and may contribute to non-responsiveness to current antidepressant therapies. Recent data have elucidated the mechanisms by which the innate and adaptive immune systems interact with neurotransmitters and neurocircuits to influence the risk for depression. Here, we detail our current understanding of these pathways and discuss the therapeutic potential of targeting the immune system to treat depression.

22 | JANUARY 2016 | VOLUME 16 www.nature.com/nri

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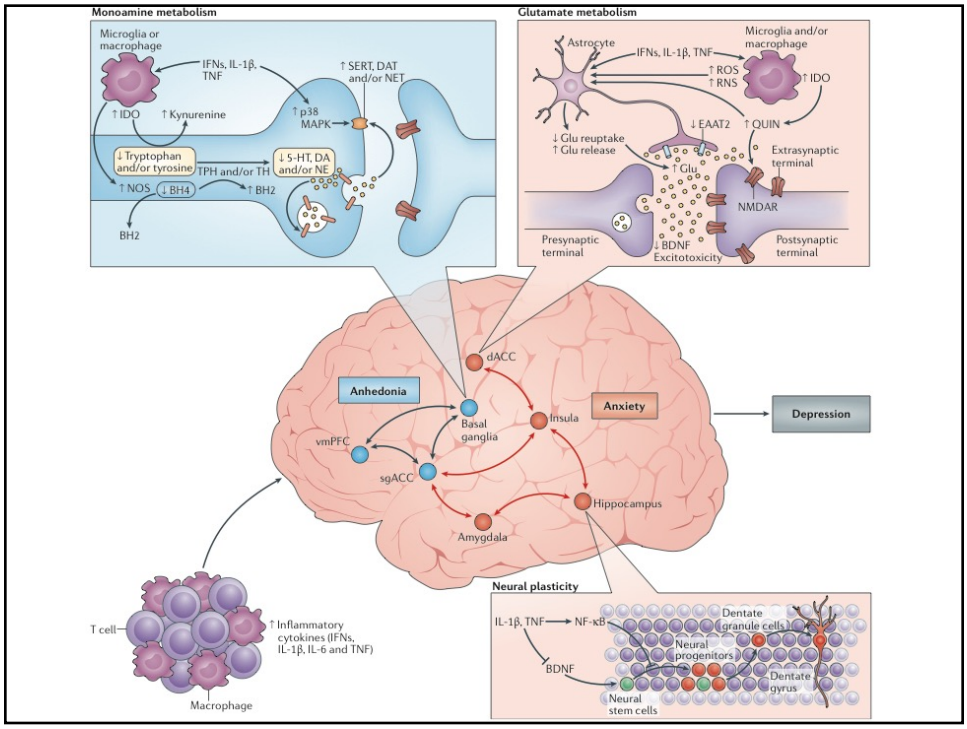

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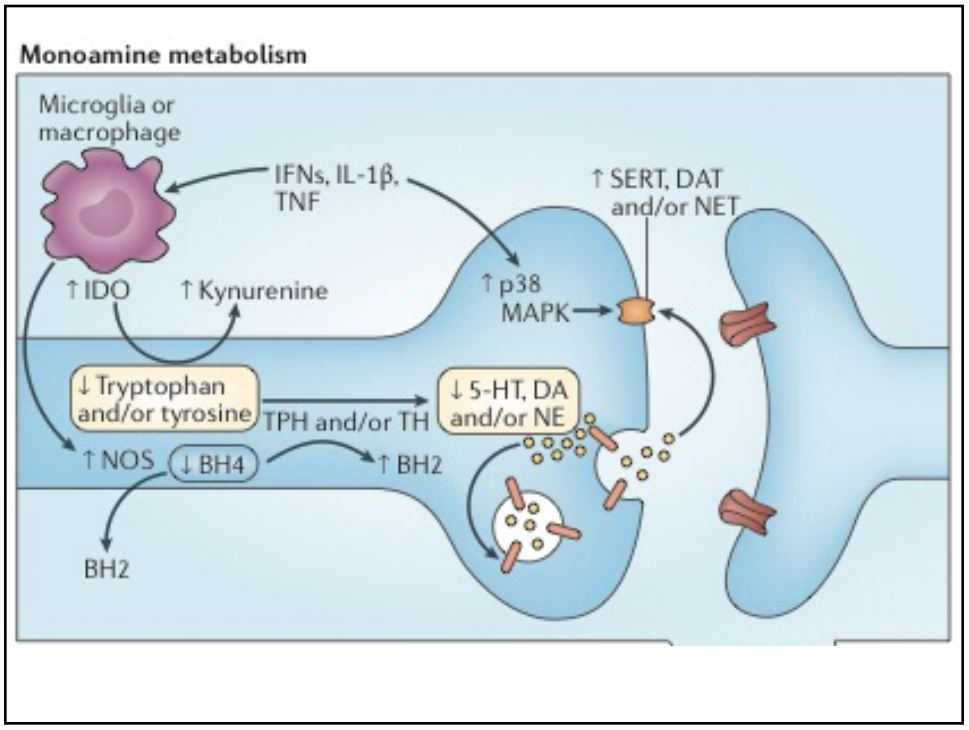

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Nerve fibers in cat knee joint

Med Articular Nerve

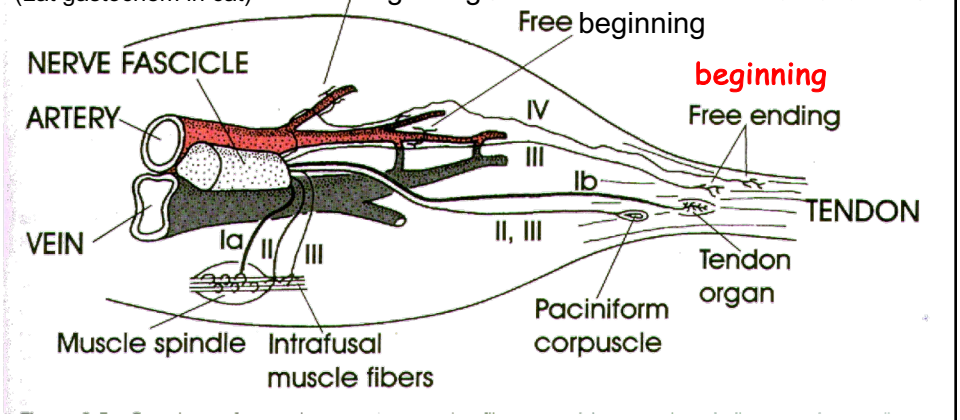
Afferents	**630 (100%)**
Group I (A-α) Fibers	0 (0%)
Group II (A-β) Fibers	59 (9%)
Group III (A-δ) Fibers	131 (21%)
Group IV (C) Fibers	440 (70%)
Efferents	
Sympathetic Fibers	500

Schmidt R, Schaible H, Mefslinger K et al. Silent and active nociceptors: structure, functions, and clinical implications. In Gebhart et al. eds. Proc 7th World Congress Pain, 1993, Paris, France. IASP Press: Seattle; 1994: p. 213-250

46

Mense S. Muscle Pain. Philadelphia: Lippincott, Williams & Wilkins; 2001: p.26-30

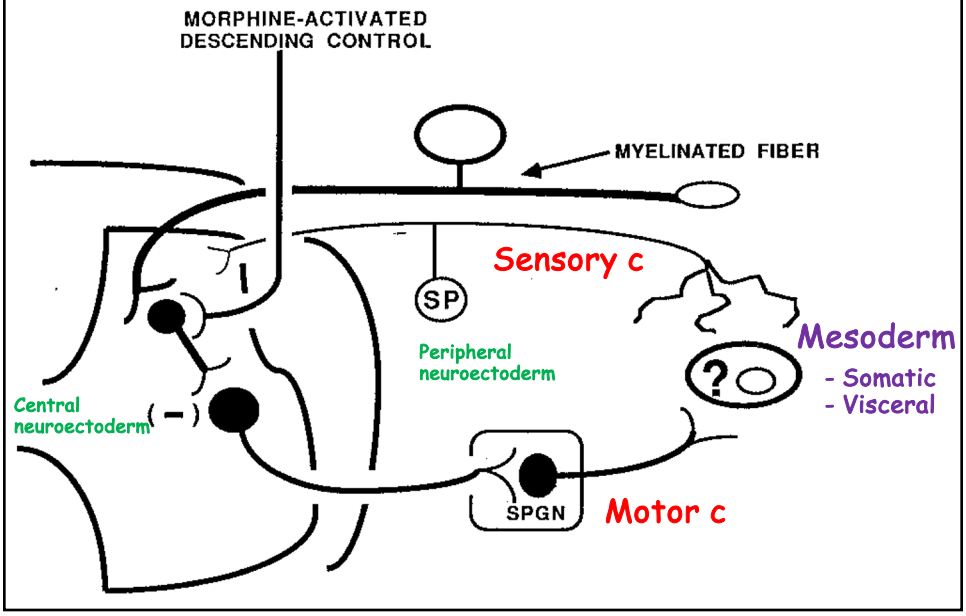
(Lat gastocnem in cat) Free beginning (Not seen α-mn, γ-mn, postgang symp C)



Motor Fibers	Sensory Fibers
α-mn - 382	Group Ia - 144 Group Ib - 72
β-mn - 14	Group II - 154
γ-mn - 324	Group III - 146 (dermis)
GR C - 1000	Group IV (C) - 1000

47

Levine JD, Cordere TJ, Basbaum AI. The peripheral nervous system and the inflammatory process. Proc Vth World Cong Pain. New York: Elsevier; 1988: p.33-43



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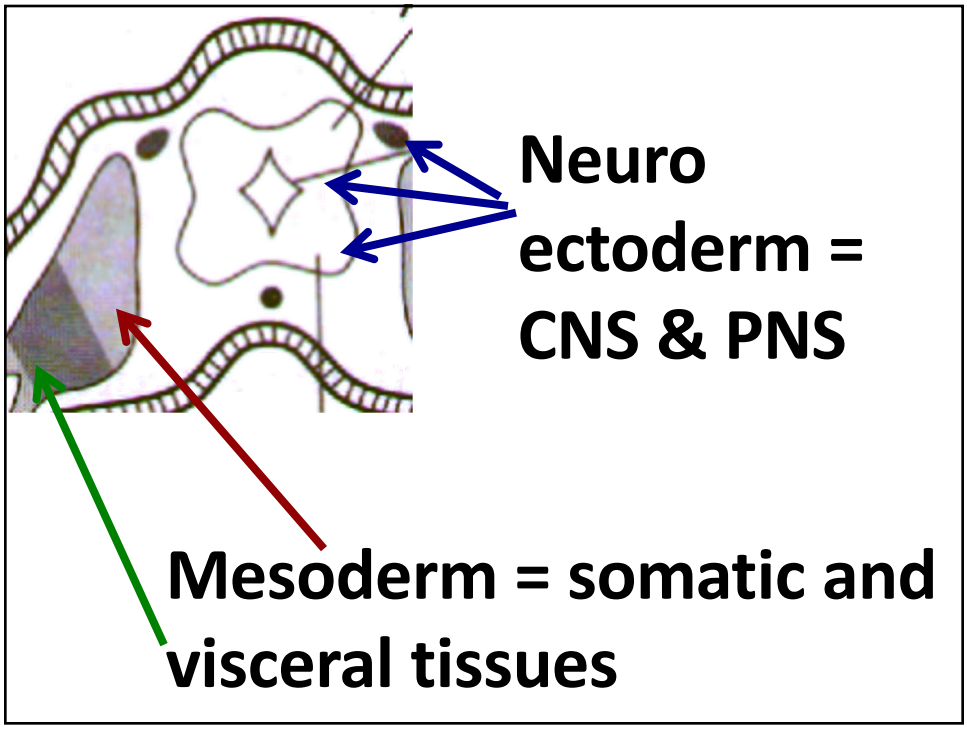
Neuro ectoderm = CNS & PNS
Mesoderm = somatic and visceral tissues

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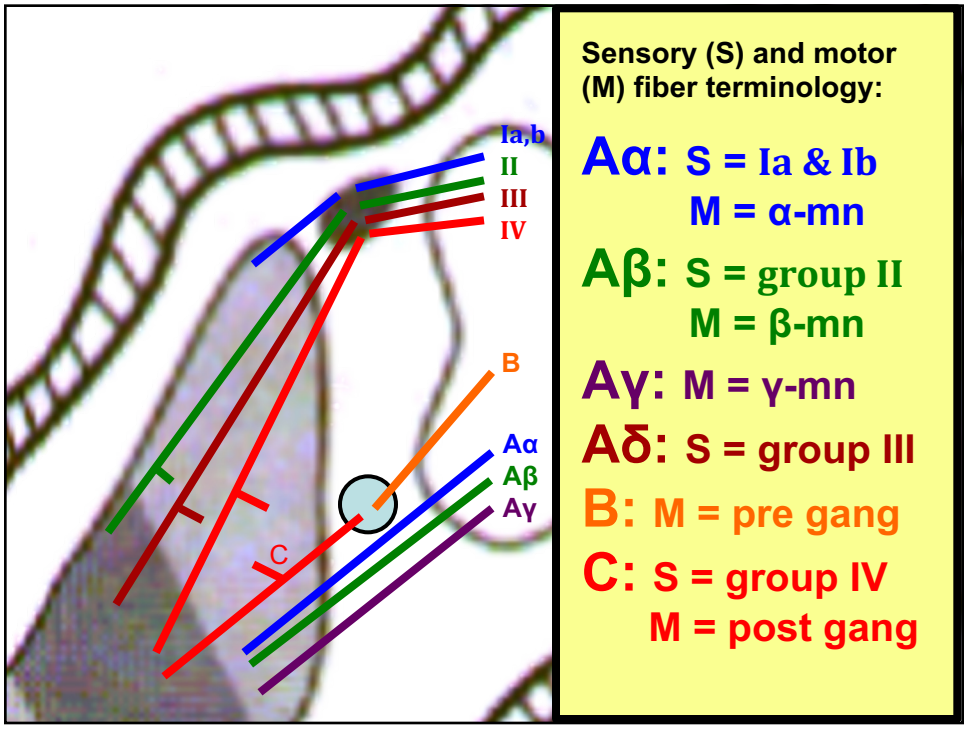
Ia,b
II
III
IV
B
Aα
Aβ
Aγ
C
Sensory (S) and motor (M) fiber terminology:
Aα: S = Ia & Ib
M = α-mn
Aβ: S = group II
M = β-mn
Aγ: M = γ-mn
Aδ: S = group III
B: M = pre gang
C: S = group IV
M = post gang

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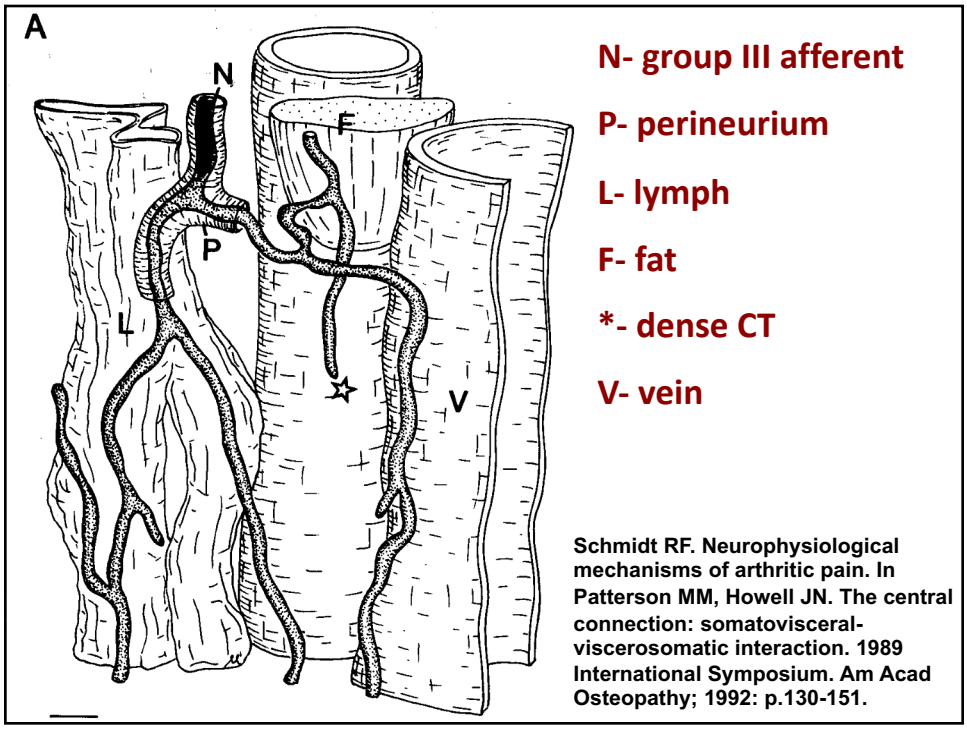
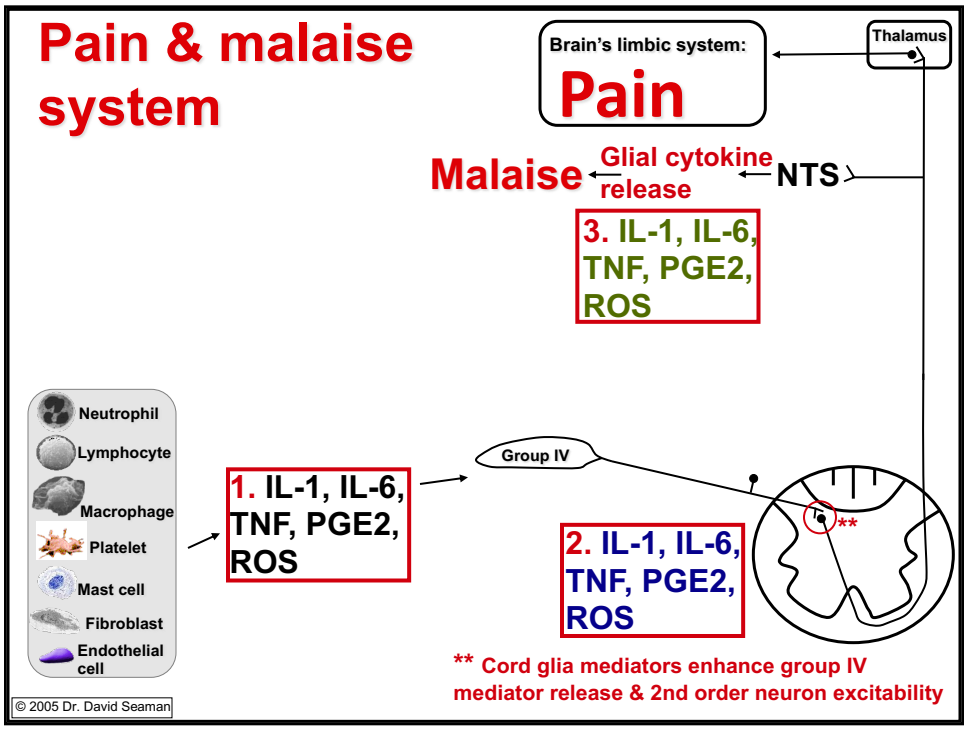

A
N
P
L
F
V
N- group III afferent
P- perineurium
L- lymph
F- fat
*- dense CT
V- vein
Schmidt RF. Neurophysiological mechanisms of arthritic pain. In Patterson MM, Howell JN. The central connection: somatovisceral-viscerosomatic interaction. 1989 International Symposium. Am Acad Osteopathy; 1992: p.130-151.

51


Pain & malaise system
Brain's limbic system:
Pain
Thalamus
Malaise
Glial cytokine release
NTS
3. IL-1, IL-6, TNF, PGE2, ROS
Neutrophil
Lymphocyte
Macrophage
Platelet
Mast cell
Fibroblast
Endothelial cell
1. IL-1, IL-6, TNF, PGE2, ROS
Group IV
2. IL-1, IL-6, TNF, PGE2, ROS
**
** Cord glia mediators enhance group IV mediator release & 2nd order neuron excitability
© 2005 Dr. David Seaman

52

We have classified these identified genes into four major clusters: genes that are able to influence:

(1) the activity of peripheral cells (e.g., monocytes) that release *proinflammatory mediators*

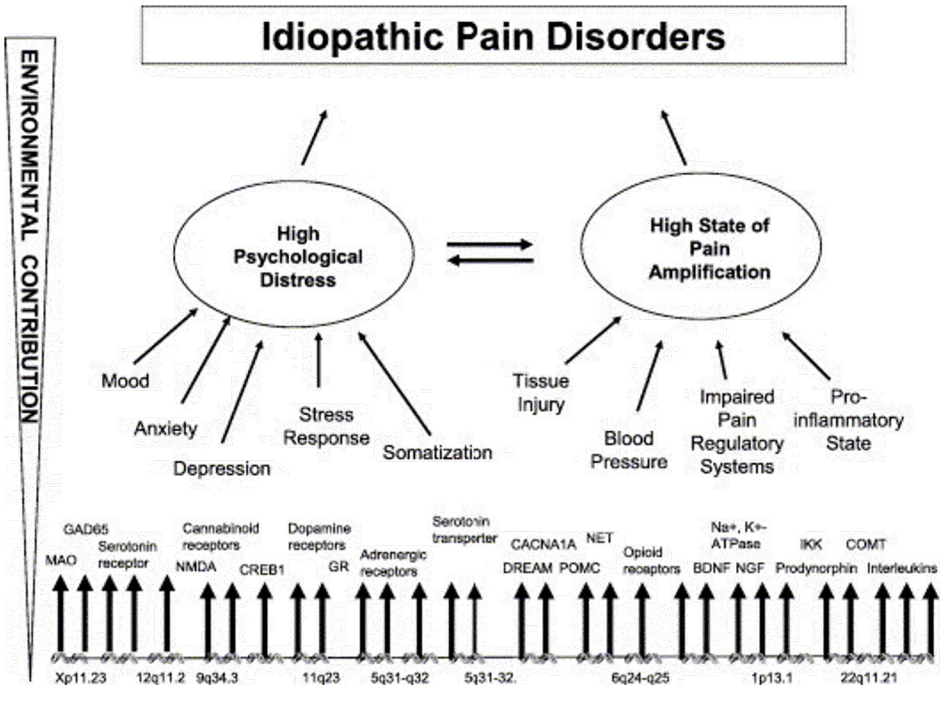
(2) the activity of nociceptive afferent fibers

(3) central nervous system pain processing systems (spinothalamic tracts and interneurons)

(4) the production of *proinflammatory mediators* from cells within the central nervous system (e.g., microglia and astrocytes)

Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders - pathways of vulnerability. Pain 2006; 123:226-30

53



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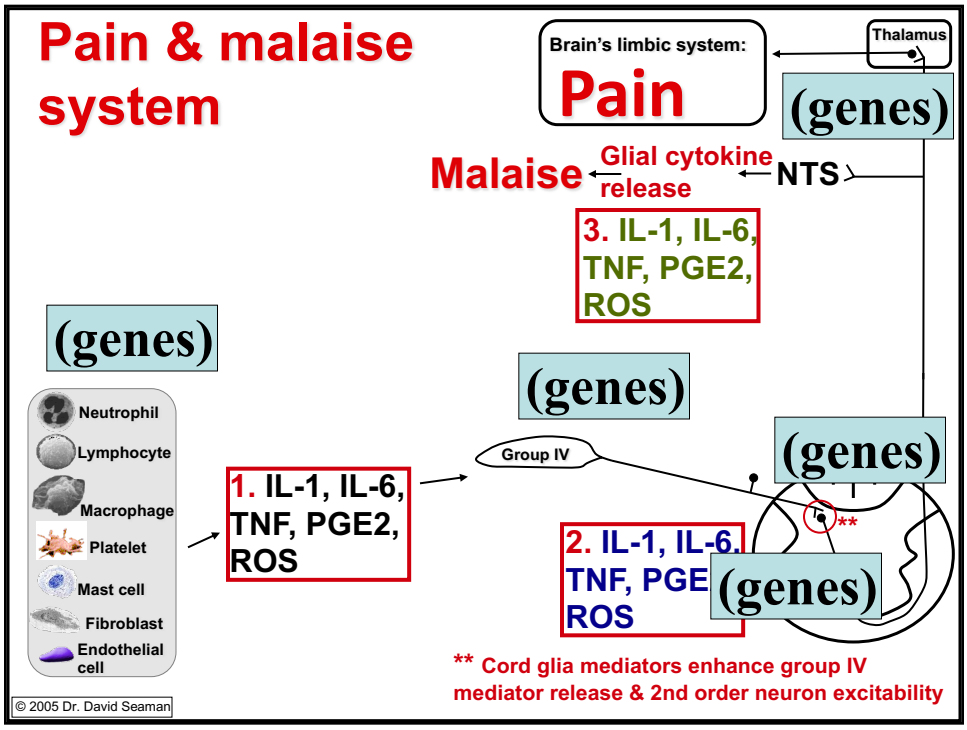
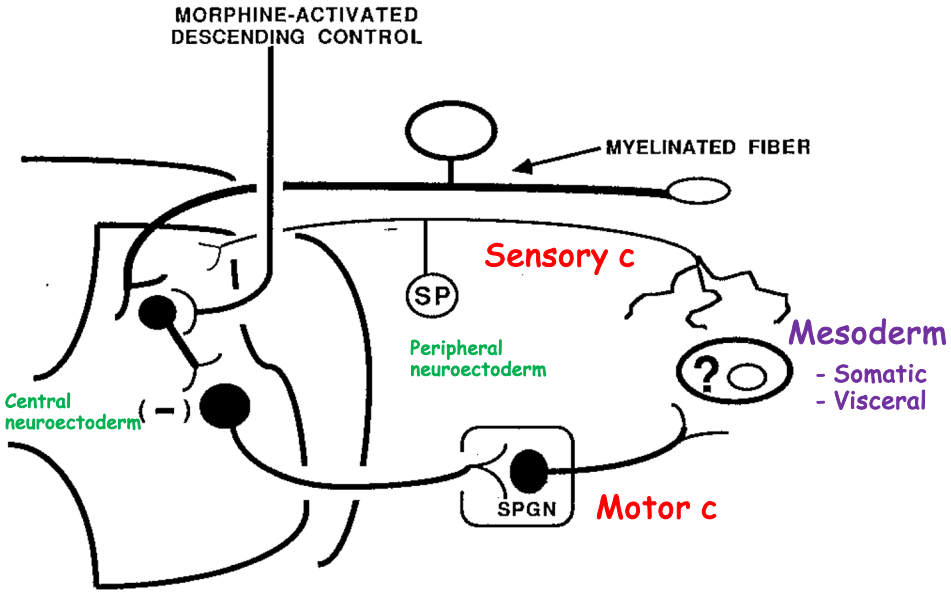


55

Levine JD, Cordere TJ, Basbaum AI. The peripheral nervous system and the inflammatory process. Proc Vth World Cong Pain. New York: Elsevier; 1988: p.33-43



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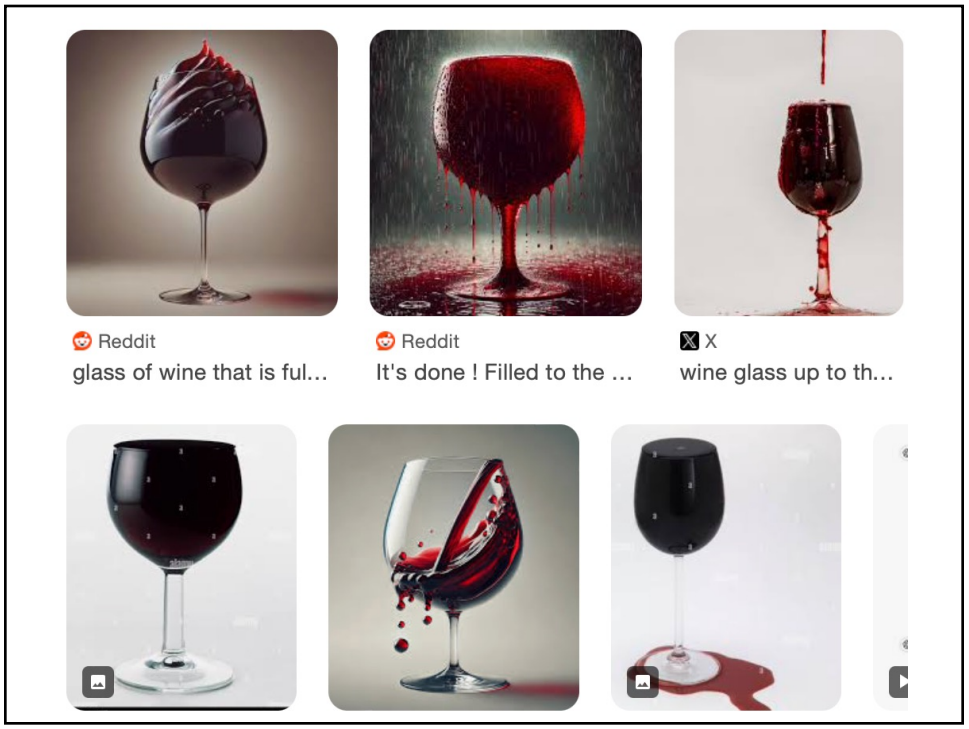
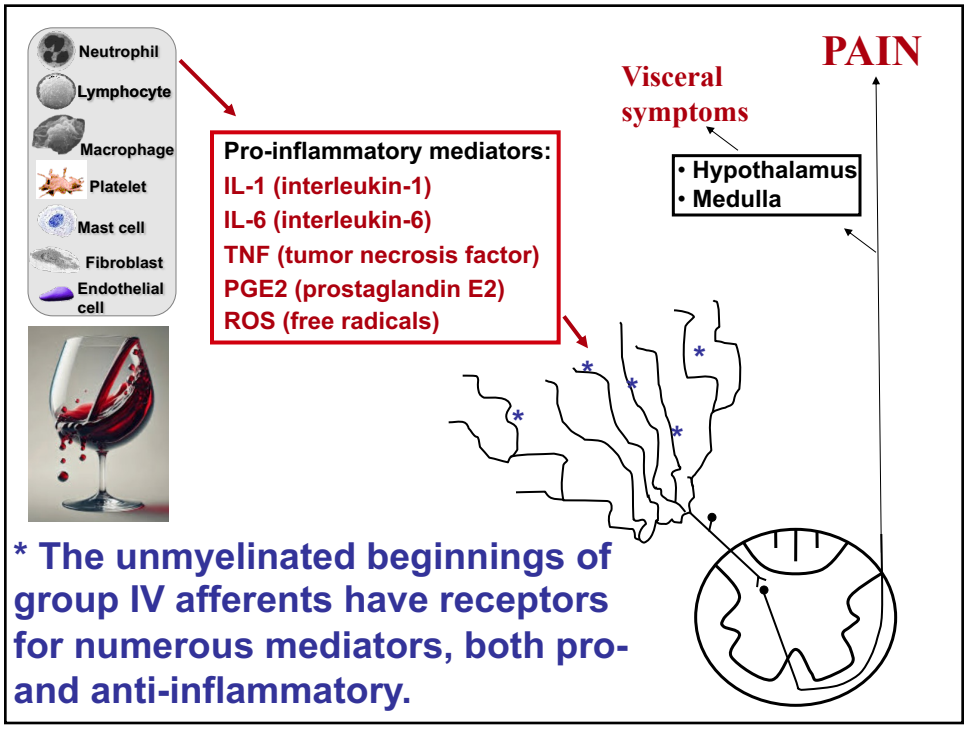
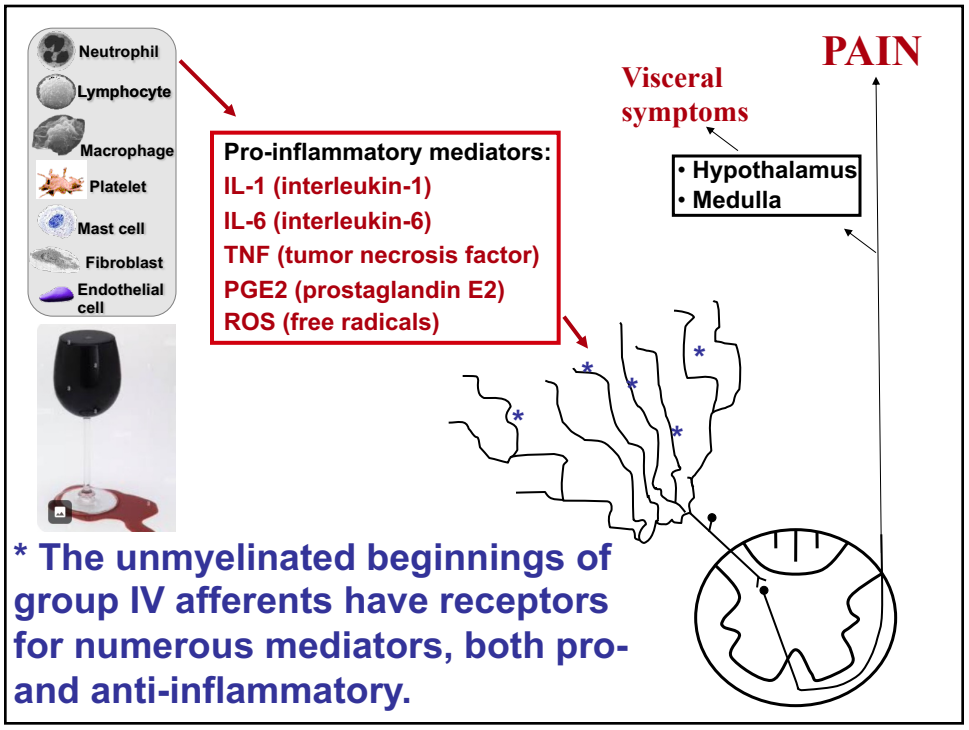

Reddit
glass of wine that is ful...
Reddit
It's done ! Filled to the ...
X
wine glass up to th...

57


Neutrophil
Lymphocyte
Macrophage
Platelet
Mast cell
Fibroblast
Endothelial cell
Pro-inflammatory mediators:
IL-1 (interleukin-1)
IL-6 (interleukin-6)
TNF (tumor necrosis factor)
PGE2 (prostaglandin E2)
ROS (free radicals)
PAIN
Visceral symptoms
• Hypothalamus
• Medulla
* The unmyelinated beginnings of group IV afferents have receptors for numerous mediators, both pro- and anti-inflammatory.

58


Neutrophil
Lymphocyte
Macrophage
Platelet
Mast cell
Fibroblast
Endothelial cell
Pro-inflammatory mediators:
IL-1 (interleukin-1)
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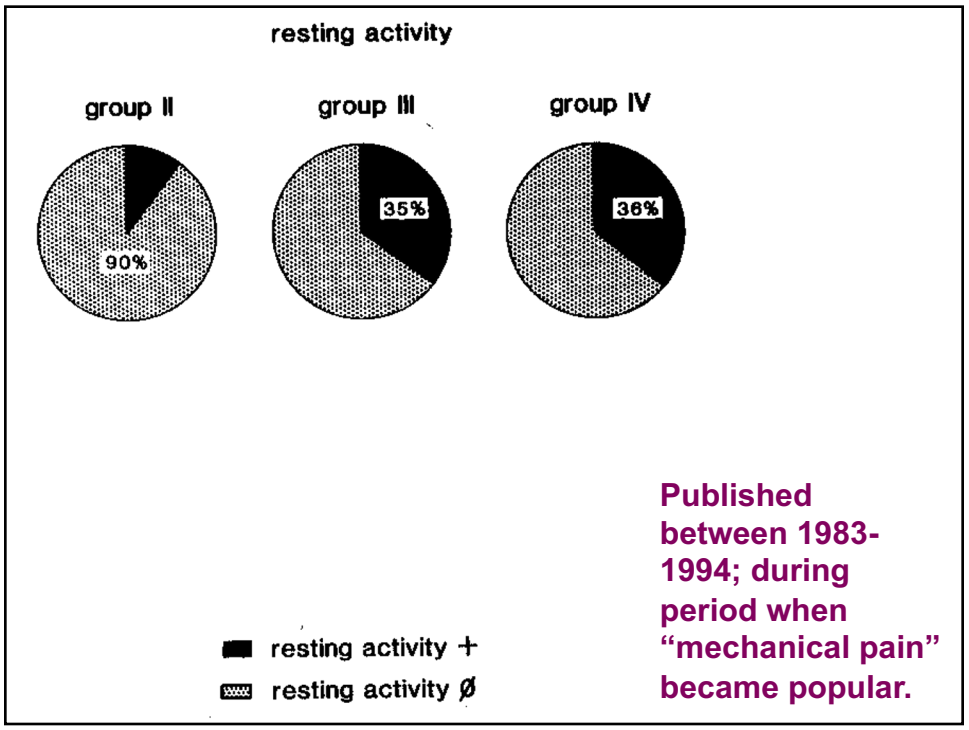
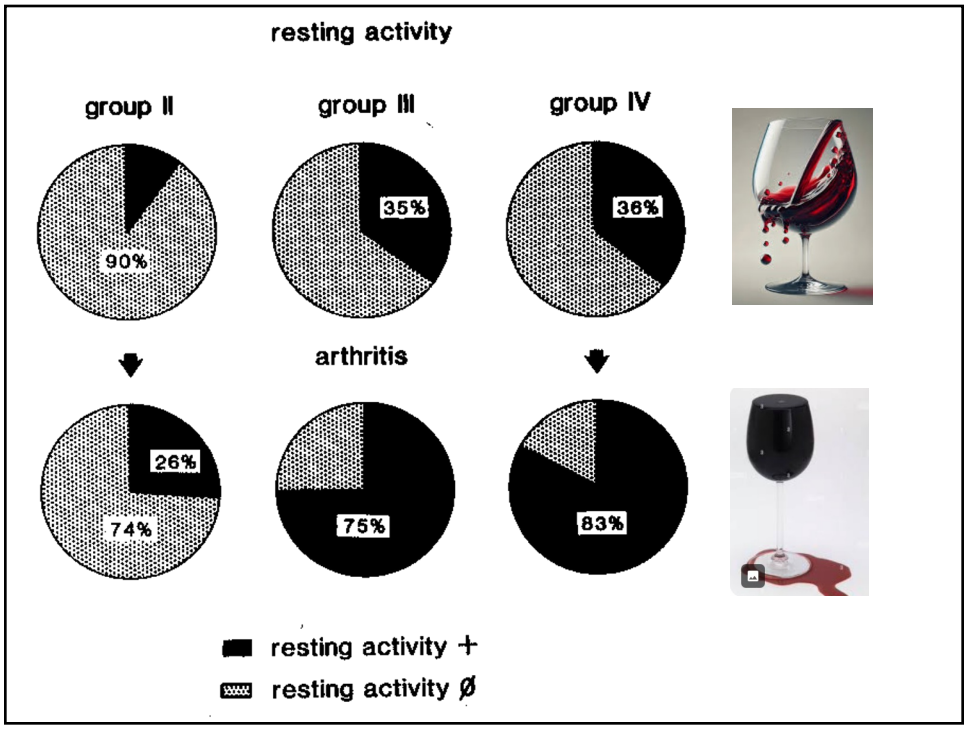
PAIN
Visceral symptoms
• Hypothalamus
• Medulla
* The unmyelinated beginnings of group IV afferents have receptors for numerous mediators, both pro- and anti-inflammatory.

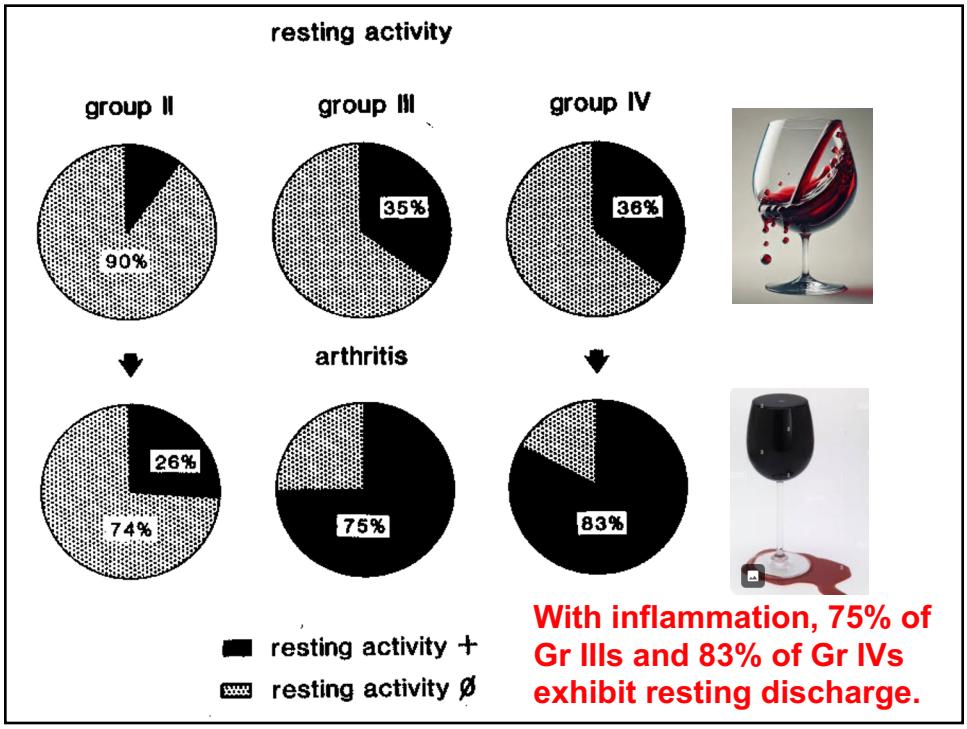
59


resting activity
group II
group III
group IV
90%
35%
36%
resting activity +
resting activity ø
Published between 1983-1994; during period when "mechanical pain" became popular.

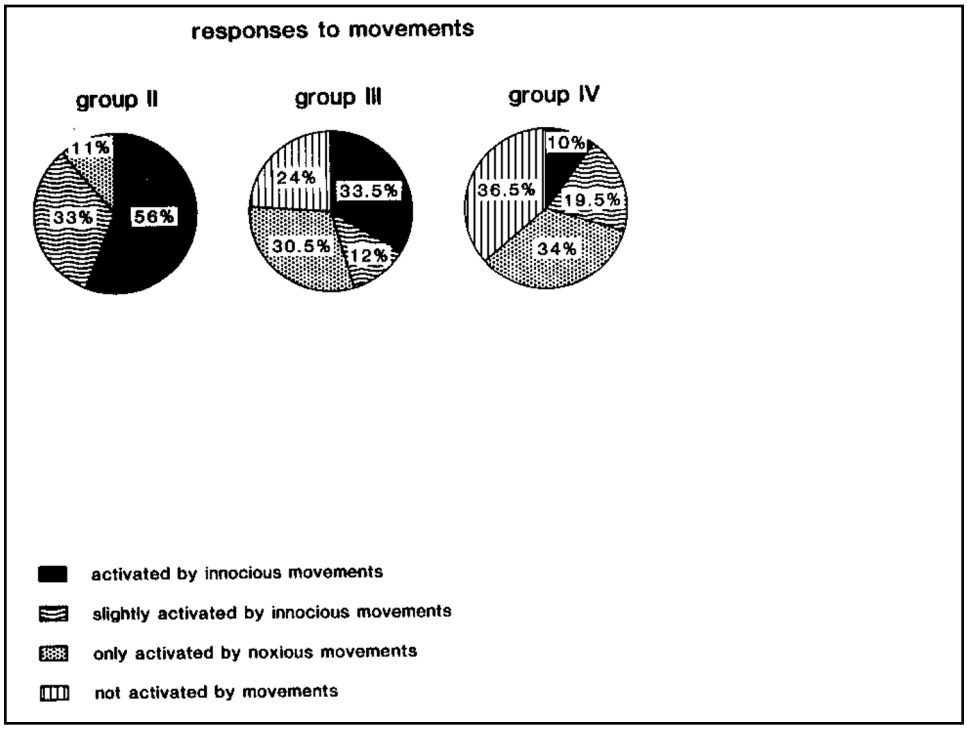
60


resting activity
group II
group III
group IV
90%
35%
36%
arthritis
26%
74%
75%
83%
resting activity +
resting activity Ø

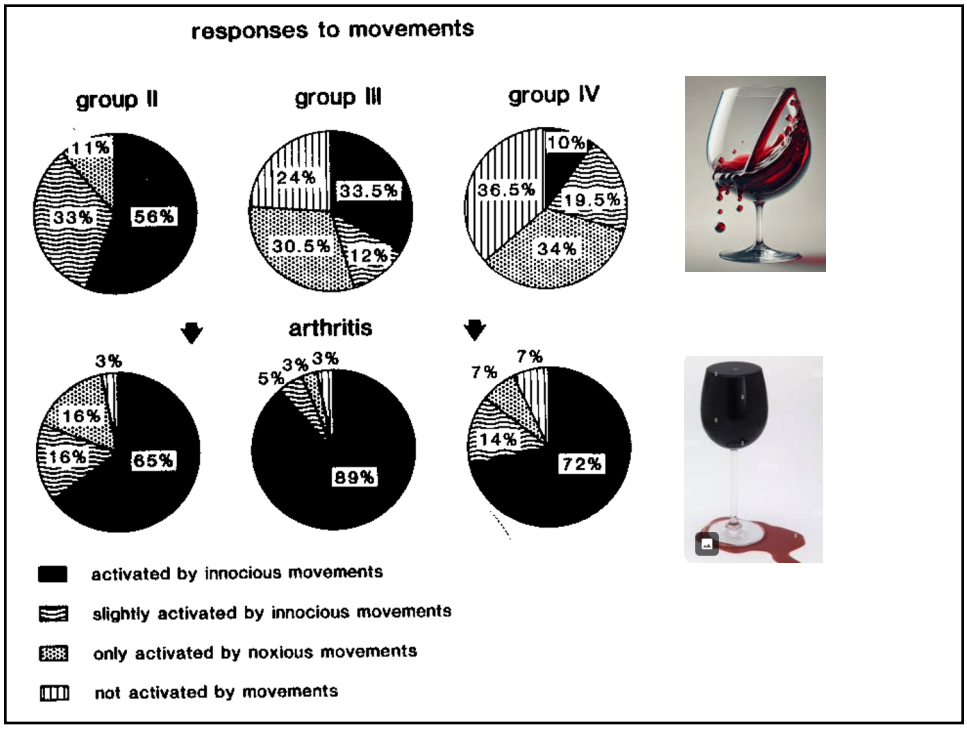
61


resting activity
group II
group III
group IV
90%
35%
36%
arthritis
26%
74%
75%
83%
resting activity +
resting activity Ø
With inflammation, 75% of Gr IIIs and 83% of Gr IVs exhibit resting discharge.

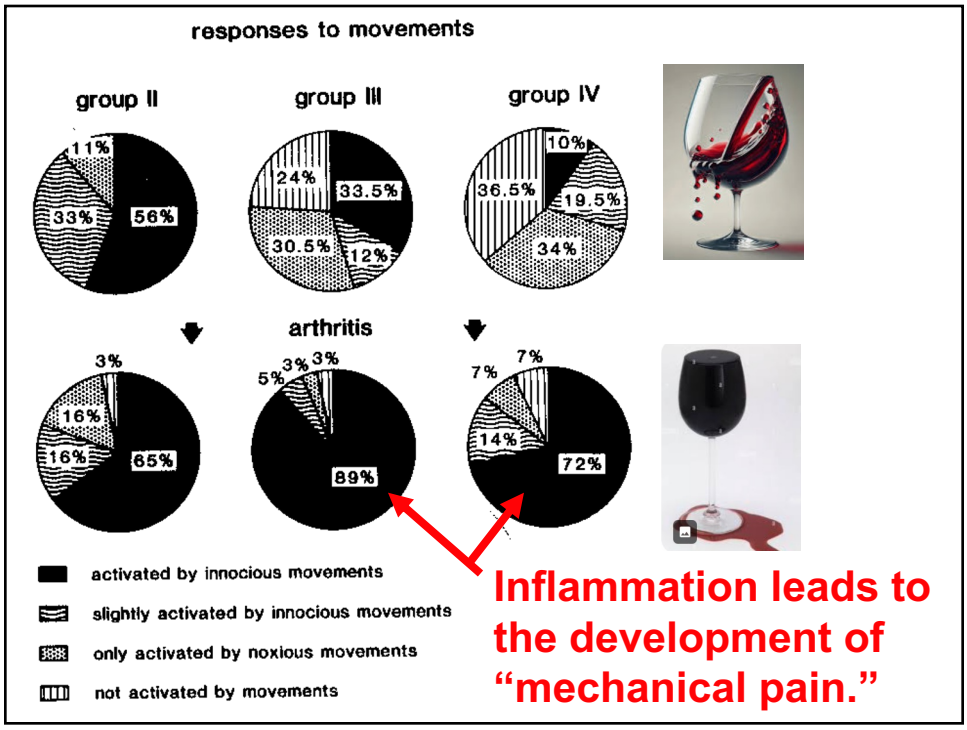
62


responses to movements
group II
group III
group IV
11%
33%
56%
24%
33.5%
30.5%
12%
10%
36.5%
19.5%
34%
activated by innocious movements
slightly activated by innocious movements
only activated by noxious movements
not activated by movements

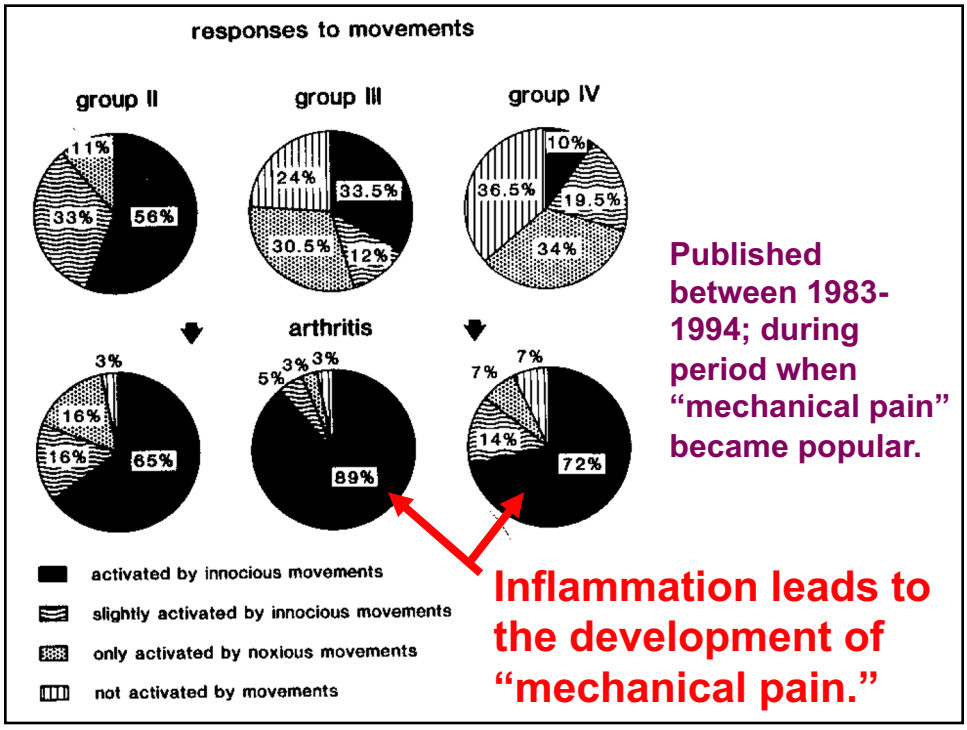
63


responses to movements
group II
group III
group IV
11%
33%
56%
24%
33.5%
30.5%
12%
10%
36.5%
19.5%
34%
arthritis
3%
16%
16%
65%
5%
3%
3%
89%
7%
7%
14%
72%
activated by innocious movements
slightly activated by innocious movements
only activated by noxious movements
not activated by movements

64


responses to movements
group II
group III
group IV
11%
33%
56%
24%
33.5%
30.5%
12%
10%
36.5%
19.5%
34%
arthritis
3%
16%
16%
65%
3%
5%
3%
89%
7%
7%
14%
72%
activated by innocious movements
slightly activated by innocious movements
only activated by noxious movements
not activated by movements
Inflammation leads to the development of "mechanical pain."

65


responses to movements
group II
group III
group IV
11%
33%
56%
24%
33.5%
30.5%
12%
10%
36.5%
19.5%
34%
arthritis
3%
16%
16%
65%
3%
5%
3%
89%
7%
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72%
activated by innocious movements
slightly activated by innocious movements
only activated by noxious movements
not activated by movements
Published between 1983-1994; during period when "mechanical pain" became popular.
Inflammation leads to the development of "mechanical pain."

66

Important Pain Terms

- *Sensitization*: abnormally low nociceptor thresholds* induced by the presence of chemical irritants, low pH, and perhaps norepinephrine

Casey K. Nociceptors and their sensitization. In Willis W. ed. Hyperalgesia and allodynia. New York: Raven Press; 1992; p.13-15

*Group IVs are actually brought closer to threshold due to the presence of pro-inflammatory chemistry.

67

Peripheral Nociceptive Sensitization

- The resting discharge of the medial articular nerve of the cat knee joint consists of some 1,800 impulses per 30-second intervals.
- During inflammation, the resting discharge increases to 11,000 impulses (60 to 367 per sec).

Schmidt RF, Schaible HG, Mefslinger K, Heppelmann, Hanesch U, Pawlak M. Silent and active nociceptors: structure, functions, and clinical implications. Proc 7th World Cong Pain. Prog Pain Res Manag Vol 2. Seattle: IASP; 1994: p.213-264

68

Peripheral Nociceptive Sensitization

- During normal movements without inflammation, some 4,400 impulses are generated over a 30-sec interval (147 per sec).
- With inflammation the same movement generated some 30,900 impulses reflecting a 7-fold increase (1030 per sec).

Schmidt RF, Schaible HG, Mefslinger K, Heppelmann, Hanesch U, Pawlak M. Silent and active nociceptors: structure, functions, and clinical implications. Proc 7th World Cong Pain. Prog Pain Res Manag Vol 2. Seattle: IASP; 1994: p.213-264

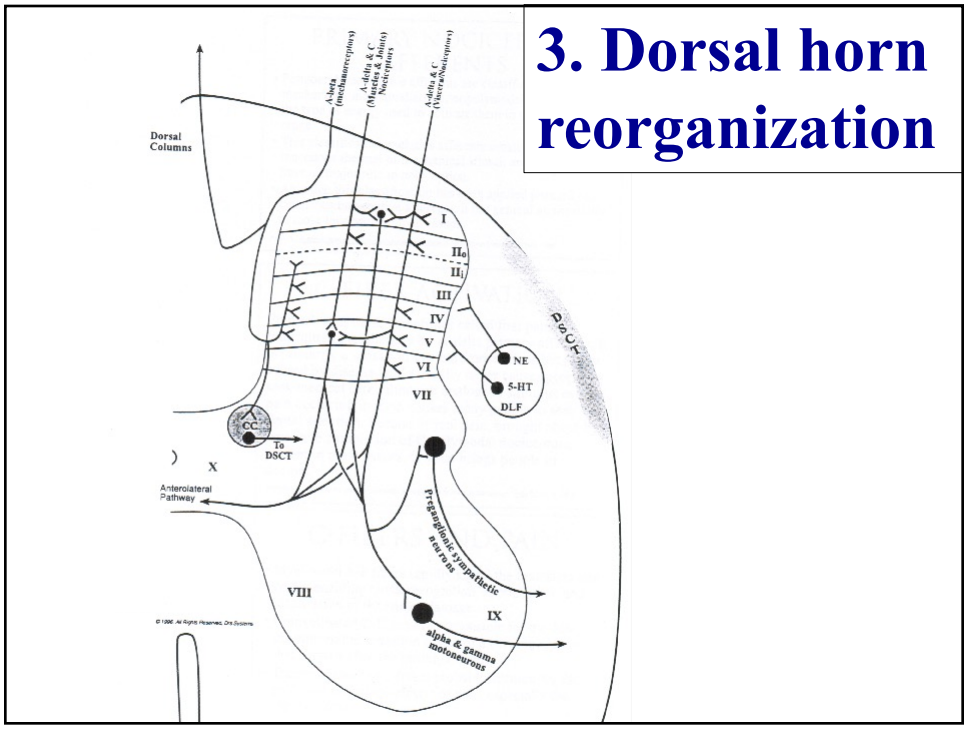
69

Causes of central sensitization

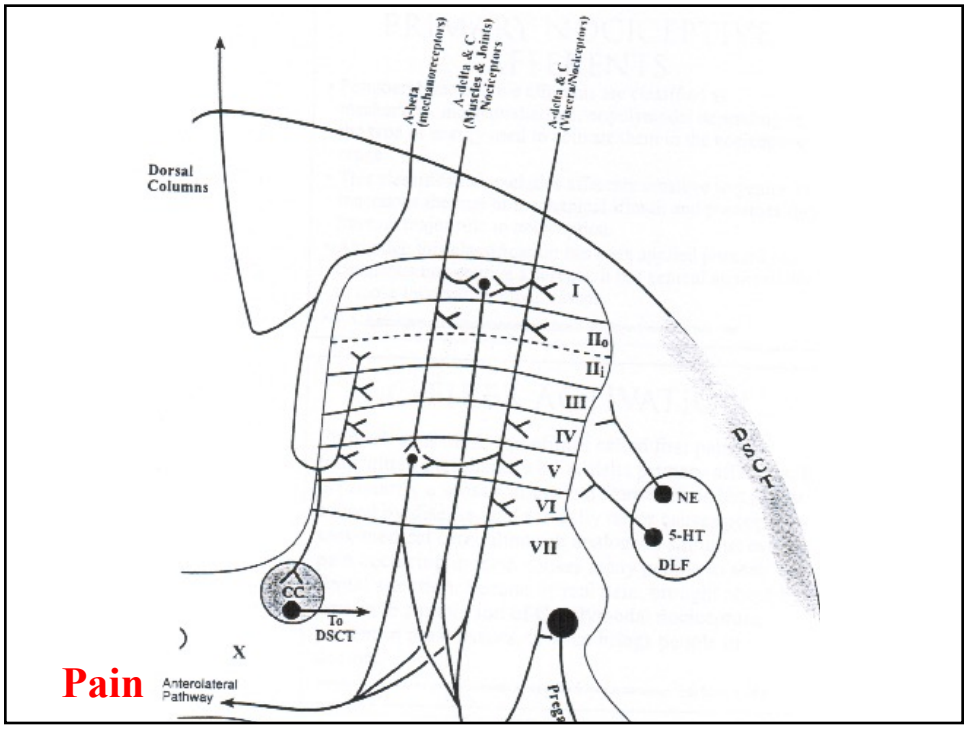
1. High intensity barrage from nociceptors
2. Glial cell activation
3. Dorsal horn reorganization
4. Phenotypic switching
5. NMDA activation

Outcome is hyperexcitable spinothalamic neurons - innocuous mechanical stimuli perceived as painful.

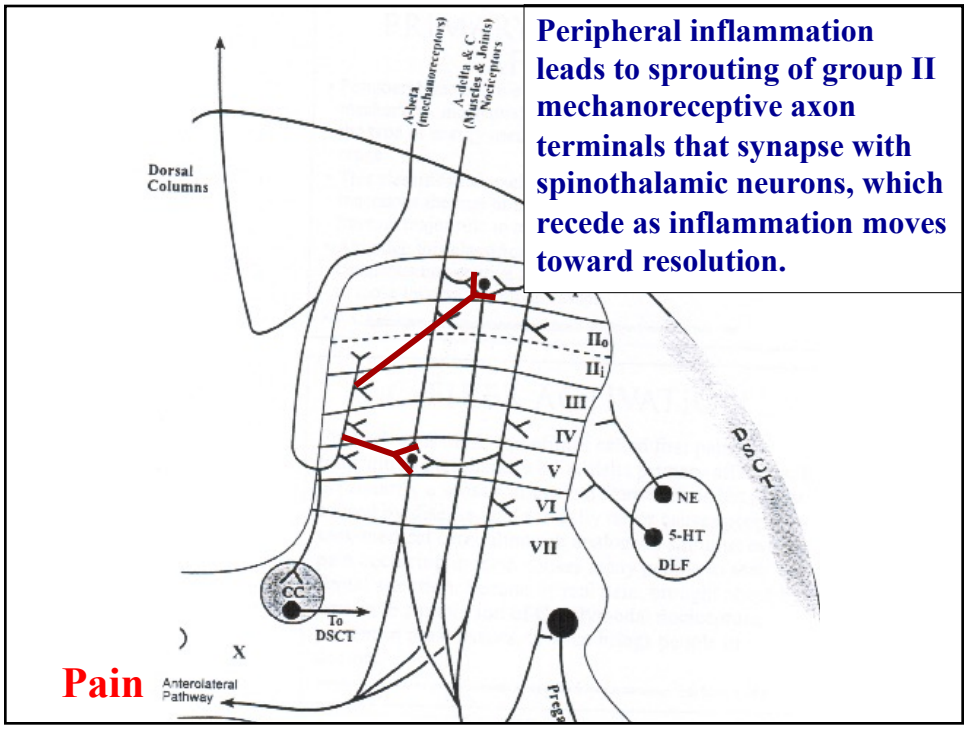
70


3. Dorsal horn reorganization
Dorsal Columns
A-beta (mechanoreceptors)
A-delta & C (Muscles & Joints) Nociceptors
A-delta & C (Viscera/Nociceptors)
I
IIo
IIi
III
IV
V
VI
VII
VIII
IX
NE
5-HT
DLF
DSCT
CC
To DSCT
X
Anterolateral Pathway
Preganglionic sympathetic neuron
alpha & gamma motoneurons

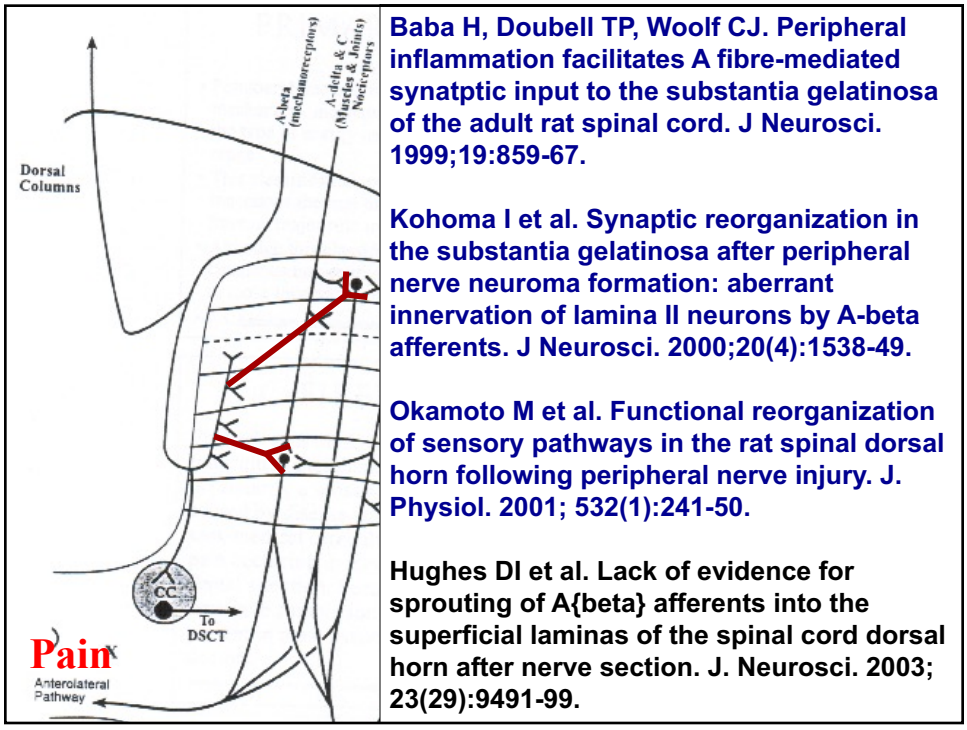
71


Dorsal Columns
A-beta (mechanoreceptors)
A-delta & C (Muscles & Joints) Nociceptors
A-delta & C (Viscera/Nociceptors)
I
IIo
IIi
III
IV
V
VI
VII
NE
5-HT
DLF
DSCT
CC
To DSCT
X
Pain
Anterolateral Pathway

72


Peripheral inflammation leads to sprouting of group II mechanoreceptive axon terminals that synapse with spinothalamic neurons, which recede as inflammation moves toward resolution.
A-beta (mechanoreceptors)
A-delta & C (Muscles & Joint(s) Nociceptors
Dorsal Columns
II0
IIi
III
IV
V
VI
VII
DSCT
NE
5-HT
DLF
CC
To DSCT
X
Pain
Anterolateral Pathway

73


Baba H, Doubell TP, Woolf CJ. Peripheral inflammation facilitates A fibre-mediated synatptic input to the substantia gelatinosa of the adult rat spinal cord. J Neurosci. 1999;19:859-67.
Kohoma I et al. Synaptic reorganization in the substantia gelatinosa after peripheral nerve neuroma formation: aberrant innervation of lamina II neurons by A-beta afferents. J Neurosci. 2000;20(4):1538-49.
Okamoto M et al. Functional reorganization of sensory pathways in the rat spinal dorsal horn following peripheral nerve injury. J. Physiol. 2001; 532(1):241-50.
Hughes DI et al. Lack of evidence for sprouting of A{beta} afferents into the superficial laminas of the spinal cord dorsal horn after nerve section. J. Neurosci. 2003; 23(29):9491-99.
A-beta (mechanoreceptors)
A-delta & C (Muscles & Joint(s) Nociceptors
Dorsal Columns
CC
To DSCT
Pain
Anterolateral Pathway

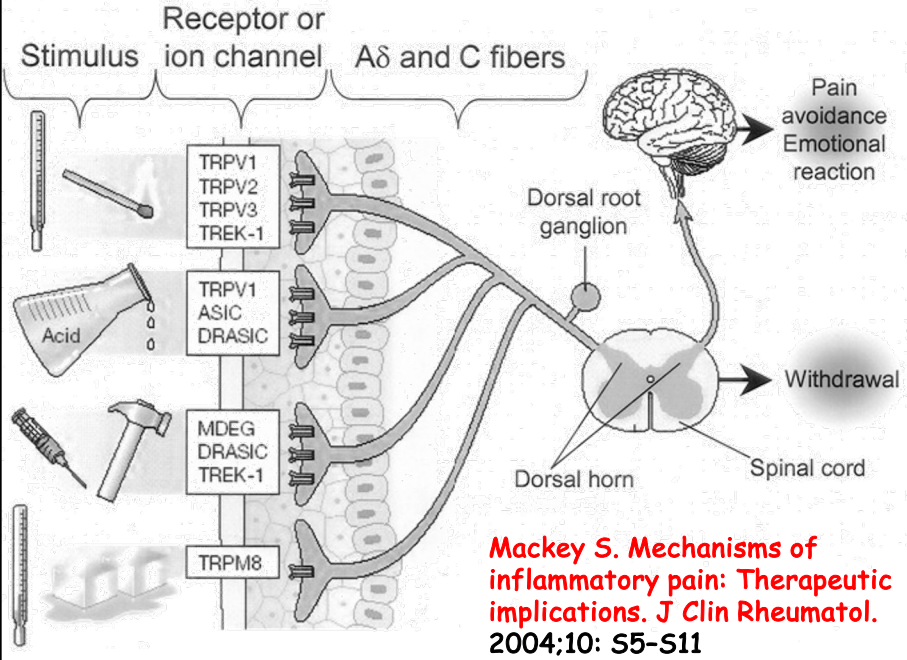
74

A-beta fiber phenotype switching…

After inflammation, there is a NGF-dependent increase in substance P expression in C fibers, but also a novel expression of this neuropeptide in some large A fibers as well.

Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. Proc Natl Acad Sci. 1999; 96(14):7723-7730

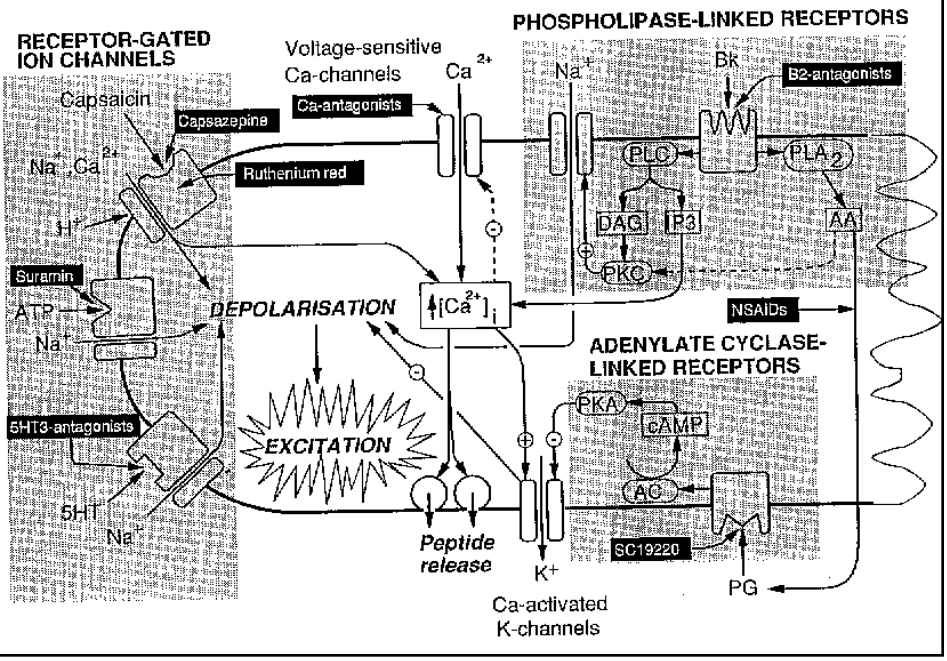
75



Mackey S. Mechanisms of inflammatory pain: Therapeutic implications. J Clin Rheumatol. 2004;10: S5-S11

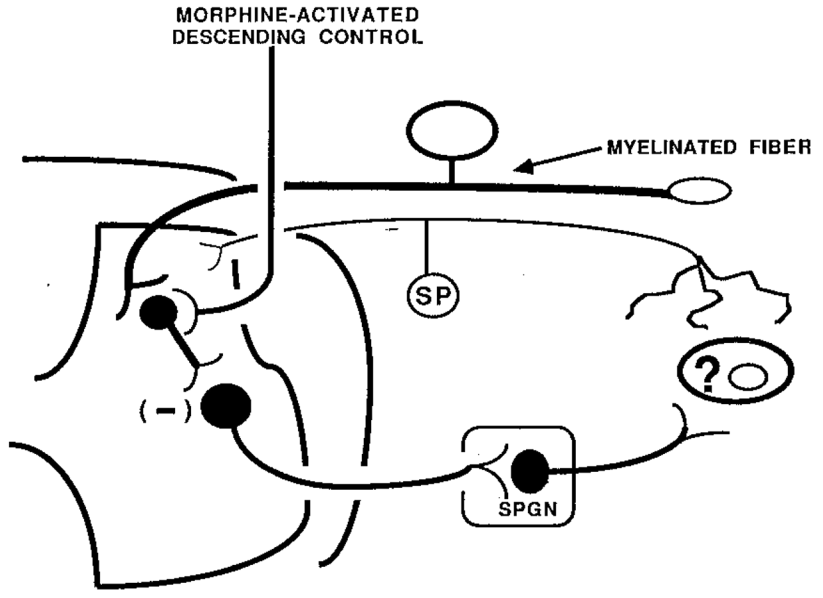
76

Melzack & Wall – Textbook of Pain, 1994



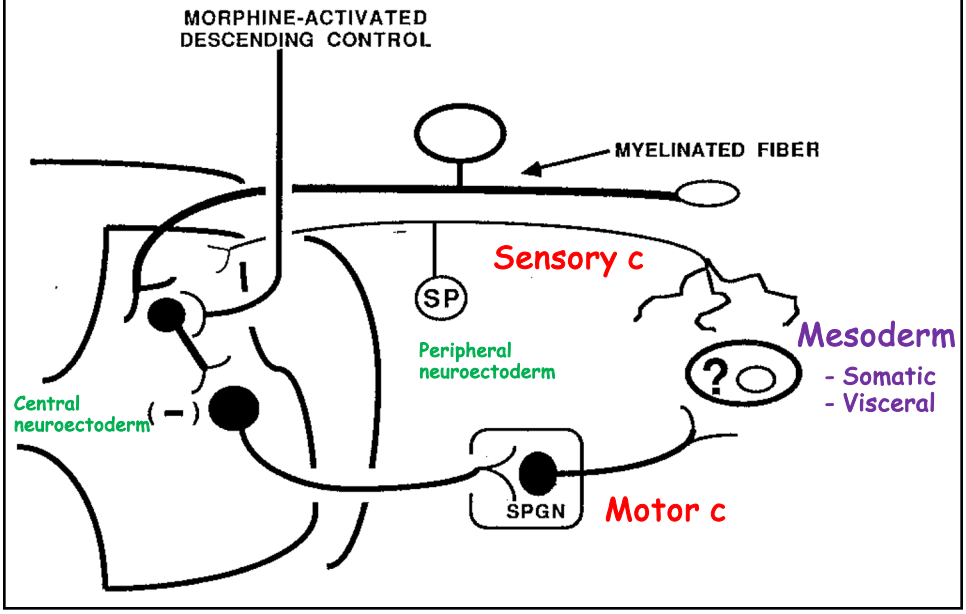
77

Levine JD, Cordere TJ, Basbaum AI. The peripheral nervous system and the inflammatory process. Proc Vth World Cong Pain. New York: Elsevier; 1988: p.33-43



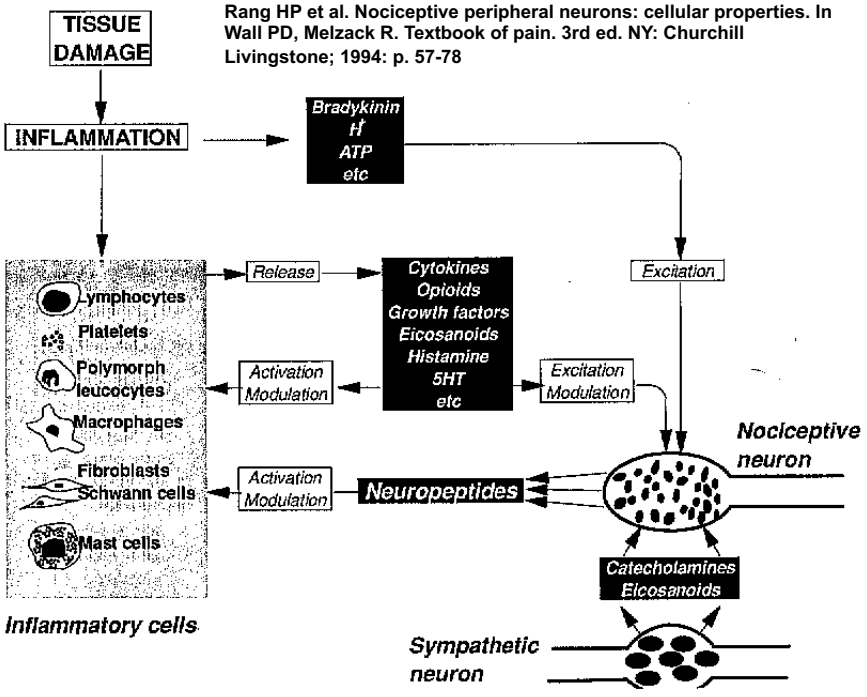
78

Levine JD, Cordere TJ, Basbaum AI. The peripheral nervous system and the inflammatory process. Proc Vth World Cong Pain. New York: Elsevier; 1988: p.33-43

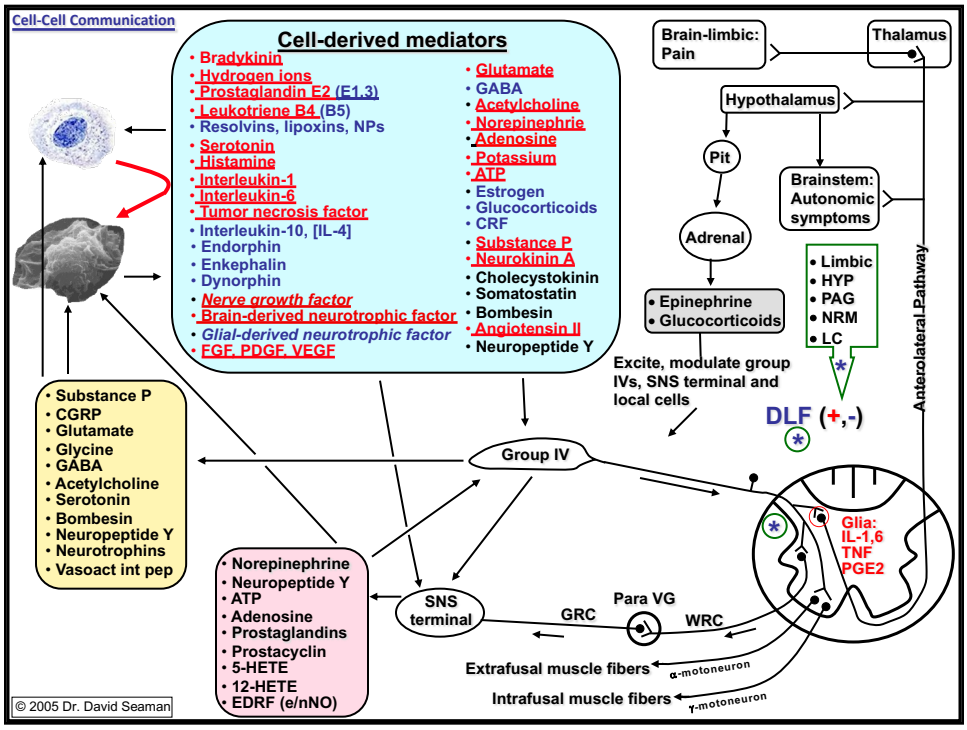


79

Rang HP et al. Nociceptive peripheral neurons: cellular properties. In Wall PD, Melzack R. Textbook of pain. 3rd ed. NY: Churchill Livingstone; 1994: p. 57-78



80


Cell-Cell Communication
Cell-derived mediators
• Bradykinin
• Hydrogen ions
• Prostaglandin E2 (E1,3)
• Leukotriene B4 (B5)
• Resolvins, lipoxins, NPs
• Serotonin
• Histamine
• Interleukin-1
• Interleukin-6
• Tumor necrosis factor
• Interleukin-10, [IL-4]
• Endorphin
• Enkephalin
• Dynorphin
• Nerve growth factor
• Brain-derived neurotrophic factor
• Glial-derived neurotrophic factor
• FGF, PDGF, VEGF
• Glutamate
• GABA
• Acetylcholine
• Norepinephrie
• Adenosine
• Potassium
• ATP
• Estrogen
• Glucocorticoids
• CRF
• Substance P
• Neurokinin A
• Cholecystokinin
• Somatostatin
• Bombesin
• Angiotensin II
• Neuropeptide Y
Brain-limbic: Pain
Thalamus
Hypothalamus
Pit
Brainstem: Autonomic symptoms
Adrenal
• Epinephrine
• Glucocorticoids
• Limbic
• HYP
• PAG
• NRM
• LC
Anterolateral Pathway
Excite, modulate group IVs, SNS terminal and local cells
DLF (+,-)
• Substance P
• CGRP
• Glutamate
• Glycine
• GABA
• Acetylcholine
• Serotonin
• Bombesin
• Neuropeptide Y
• Neurotrophins
• Vasoact int pep
Group IV
Glia: IL-1,6 TNF PGE2
• Norepinephrine
• Neuropeptide Y
• ATP
• Adenosine
• Prostaglandins
• Prostacyclin
• 5-HETE
• 12-HETE
• EDRF (e/nNO)
SNS terminal
GRC
Para VG
WRC
Extrafusal muscle fibers
α-motoneuron
Intrafusal muscle fibers
γ-motoneuron
© 2005 Dr. David Seaman

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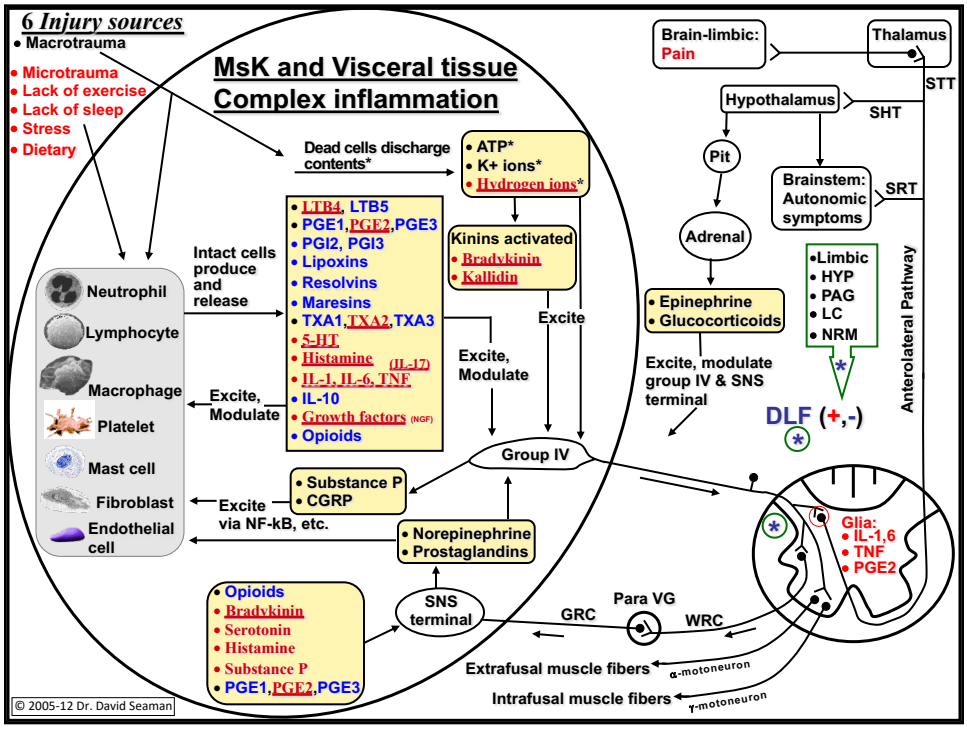
6 Injury sources
• Macrotrauma
• Microtrauma
• Lack of exercise
• Lack of sleep
• Stress
• Dietary
MsK and Visceral tissue Complex inflammation
Dead cells discharge contents*
• ATP*
• K+ ions*
• Hydrogen ions*
Kinins activated
• Bradykinin
• Kallidin
Intact cells produce and release
• LTB4, LTB5
• PGE1, PGE2, PGE3
• PGI2, PGI3
• Lipoxins
• Resolvins
• Maresins
• TXA1, TXA2, TXA3
• 5-HT
• Histamine (IL-17)
• IL-1, IL-6, TNF
• IL-10
• Growth factors (NGF)
• Opioids
Excite
Excite, Modulate
Excite, Modulate
Neutrophil
Lymphocyte
Macrophage
Platelet
Mast cell
Fibroblast
Endothelial cell
Brain-limbic: Pain
Thalamus
STT
Hypothalamus
SHT
Pit
Brainstem: Autonomic symptoms
SRT
Adrenal
• Epinephrine
• Glucocorticoids
•Limbic
• HYP
• PAG
• LC
• NRM
Anterolateral Pathway
Excite, modulate group IV & SNS terminal
DLF (+,-)
Group IV
• Substance P
• CGRP
Excite via NF-kB, etc.
• Norepinephrine
• Prostaglandins
Glia:
• IL-1,6
• TNF
• PGE2
• Opioids
• Bradykinin
• Serotonin
• Histamine
• Substance P
• PGE1, PGE2, PGE3
SNS terminal
GRC
Para VG
WRC
Extrafusal muscle fibers
α-motoneuron
Intrafusal muscle fibers
γ-motoneuron
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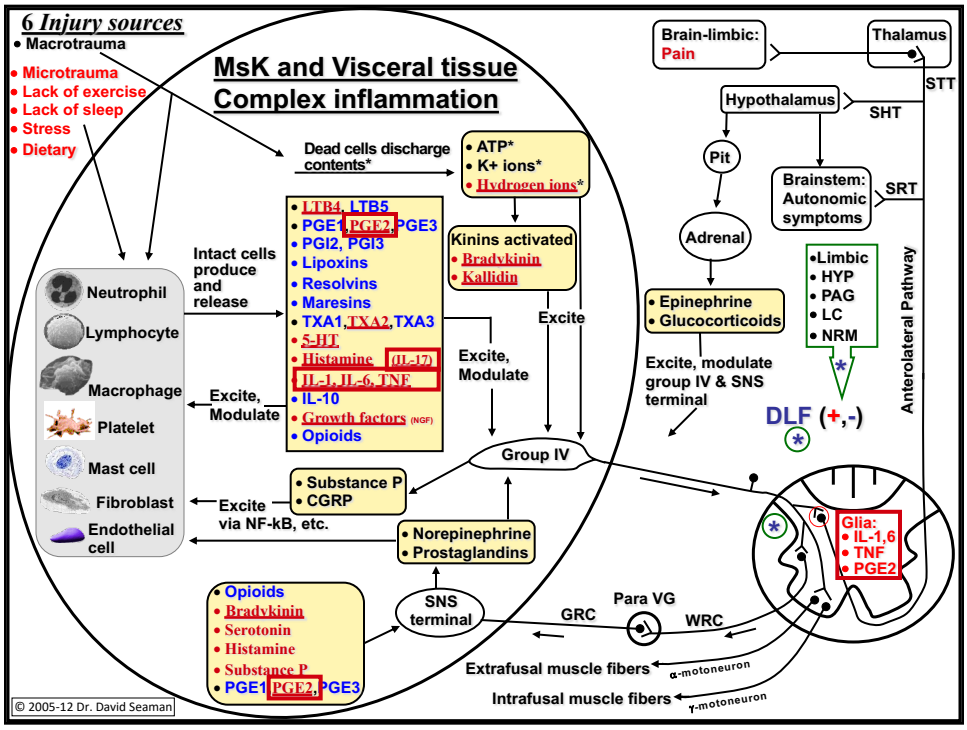
82



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Questions and Discussion

- Thoughts?
- Pain generators?
- Neurologic compromise?
- Pain biomarkers?
- Means to objectively measure pain and mitigation through chiropractic?
- Future research?

84

Upcoming Grand Rounds Schedule

The First Tuesday of the Month at 8PM EST

Upcoming Rounds

- May 6, 2025 – Radiology Errors – Cliff Tao, DC, DACBR
- June 3, 2025 – Chiropractic Adjustments and IVD Herniations

POSTGRADDC
EVIDENCE BASED, CLINICALLY INTUITIVE CE

85

The PostGradDC Certifications

The PostGradDC Certifications

- Our **PostGradDC Certifications**
- Our coursework is approved by the **American College of Chiropractic Orthopedists**, and the **International Academy of Neuromusculoskeletal Medicine** and **PACE**.
- Each certification entails **10 CE hours** of designated recorded and live coursework.

POSTGRADDC
EVIDENCE BASED, CLINICALLY INTUITIVE CE

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Credit

- **You must complete the Class Survey** to receive your Certificate of Completion and license renewal credit (for those doctors practicing in PACE approved states):
  - Go to **PostGradDC.com**, log onto your account, go to **My Account** and click on the class.
  - **Complete the survey.**
    - Click **'Submit.'**
    - On the next page to appear, click **'Mark Complete.'**
  - Your class certificate will be available under your account.

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Thank you!

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