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Focus Article

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Central Sensitization and $Ca_v\alpha_2\delta$ Ligands in Chronic Pain Syndromes: Pathologic Processes and Pharmacologic Effect

Michael Tuchman, Jeannette A. Barrett, Sean Donevan, Thomas G. Hedberg, and Charles P. Taylor

This focus article discusses how the central nervous system plasticity phenomenon, central sensitization, is established in the induction and maintenance of chronic pain, allodynia, and hyperalgesia. In addition, it explores the neurophysiologic actions of the calcium-channel ligands gabapentin and pregabalin in limiting pathological manifestations of central sensitization.

Original Reports

1250

Electroacupuncture Increases CB2 Receptor Expression on Keratinocytes and Infiltrating Inflammatory Cells in Inflamed Skin Tissues of Rats

Jing Zhang, Lin Chen, Tangfeng Su, Fuyuan Cao, Xianfang Meng, Lei Pei, Jing Shi, Hui-Lin Pan, and Man Li

Endogenous cannabinoids and peripheral cannabinoid CB2 receptors are involved in the antinociceptive effect of electroacupuncture on inflammatory pain. To study this, inflammatory pain was induced by local injection of complete Freund's adjuvant into the hindpaw of rats. Findings show that electroacupuncture increases the CB2 receptor expression on keratinocytes and infiltrates inflammatory cells in inflammatory skin tissues. This finding provides new evidence showing the potential role of CB2 receptors in the analgesic effect of acupuncture.

ON THE COVER

This image shows effects of inflammation and electroacupuncture treatments on keratinocytes labeled with cannabinoid CB2 receptor immunoreactivity in skin tissues. This report discusses the role of CB2 receptors in the effect of acupuncture on inflammatory pain. See Zhang, et al, page 1250.

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1259 **Assessing Pain in Older People With Persistent Pain: The NRS Is Valid But Only Provides Part of the Picture**

Bradley M. Wood, Michael K. Nicholas, Fiona Blyth,
Ali Asghari, and Stephen Gibson

This study examined the assessment of pain intensity and pain distress with the Numerical Rating Scale (NRS) in a sample of 800 elderly patients (ages 60 and older) with persistent pain. This confirms the utility of the NRS as a measure of pain intensity and pain distress in elderly patients with persistent pain.

1267 **Positive Affect Mediates the Relationship Between Pain-Related Coping Efficacy and Interference in Social Functioning**

Soo Hyun Park and Nomita Sonty

Emotional states have been shown to influence resilient behavior in conditions of loss, bereavement, and stress. Positive affect has been associated with better health outcomes, including in chronic pain. This study examined the role of positive versus negative emotions in the association between pain-related coping efficacy and interference with social functioning in a sample of chronic pain patients.

1274 **Antagonistic Effects of Ondansetron and Tramadol? A Randomized Placebo and Active Drug Controlled Study**

Neele I. Rauers, Frank Stüber, Eun-Hae Lee, Frank Musshoff,
Rolf Fimmers, Martin Barann, and Ulrike M. Stamer

Opposing effects of ondansetron and tramadol on the serotonin pathway have been suggested, which possibly increase tramadol consumption and emesis when co-administered. In a randomized, double-blinded study, tramadol consumption and response to antiemetic treatment were compared. Tramadol consumption did not differ between the groups. The authors conclude that co-medication of these drugs neither increased postoperative analgesic consumption nor frequency of emesis.

1282

Duloxetine Versus Placebo in Patients With Chronic Low Back Pain: A 12-Week, Fixed-Dose, Randomized, Double-Blind Trial

Vladimir Skljarevski, Shuyu Zhang, Durisala Desaiyah, Karla J. Alaka, Santiago Palacios, Tomasz Miazgowski, and Kyle Patrick

This research assessed efficacy and safety of duloxetine in patients with chronic low back pain. Adults were treated with either duloxetine 60 mg once daily or placebo for 12 weeks. The primary measure was Brief Pain Inventory average pain. This study provides clinical evidence of the efficacy and safety of duloxetine for low back pain.

1291

How Do Parents of Preverbal Children With Acute Otitis Media Determine How Much Ear Pain Their Child Is Having?

Nader Shaikh, Diana H. Kearney, D. Kathleen Colborn, Tracy Balentine, Wentao Feng, Yan Lin, and Alejandro Hoberman

How do parents of preverbal children determine whether a child is suffering from ear aches? Authors constructed 8 cases describing a 1-year-old child with acute otitis media using combinations of 6 observable symptoms. Parents were asked to assign a pain level to each case on a visual analog scale. Higher levels of parental education and private insurance were associated with higher reported pain levels. Thus, the authors question the utility of an overall pain score from a 1-item parent scale.

1295

Referred Pain from Muscle Trigger Points in the Masticatory and Neck-Shoulder Musculature in Women With Temporomandibular Disorders

César Fernández-de-las-Peñas, Fernando Galán-del-Río, Cristina Alonso-Blanco, Rodrigo Jiménez-García, Lars Arendt-Nielsen, and Peter Svensson

Temporomandibular disorder includes different conditions involving the temporomandibular joint and the masticatory muscles. This work describes the referred pain patterns and areas of trigger points in the masticatory and neck-shoulder muscles of women with myofascial temporomandibular disorders. The results agree with the notion of peripheral and central sensitization mechanisms in patients with myofascial temporomandibular disorder.

1305 **Large and Small Fiber Dysfunction in Peripheral Nerve Injuries With or Without Spontaneous Pain**

Inge Petter Kleggetveit and Ellen Jørum

The role of small fiber damage in patients with peripheral nerve injuries with and without spontaneous pain was explored. The function of large myelinated nerve fibers, as well as small nerve fibers in patients with peripheral nerve injuries, patients with spontaneous pain, and patients without pain were examined. Small fiber function did not significantly differ between patients with and without pain, suggesting elevated thermal thresholds alone will not reflect mechanisms responsible for pain. Hyperphenomena were present in the affected pain group only.

1311 **Initial Psychometric Properties of the Pain Care Quality Survey (PainCQ)**

Susan L. Beck, Gail L. Towsley, Marjorie A. Pett, Patricia H. Berry, Ellen Lavoie Smith, Jeannine M. Brant, and Jia-Wen Guo

The psychometric properties of the Pain Care Quality survey, a new instrument to measure the quality of nursing and interdisciplinary care related to pain management, were examined. Hospitalized medical/surgical oncology patients from 3 states completed the 44-item version of the survey. This tool can be used for research and as a clinical performance measure to monitor and improve quality of care and patient outcomes.

1320 **Risk Factors Predicting the Development of Widespread Pain From Chronic Back or Neck Pain**

Lindsay L. Kindler, Kim D. Jones, Nancy Perrin, and Robert M. Bennett

Emerging evidence suggests that some individuals with regional pain disorders go on to develop chronic widespread pain. However, the mechanism behind this transition and nature of risk factors that predispose a person to develop widespread pain remain to be elucidated. The purpose of this study was to describe the frequency with which participants with chronic back or neck pain develop chronic widespread pain, and to determine the risk factors associated with this development.

1329

Relationship Between Fibromyalgia and Obesity in Pain, Function, Mood, and Sleep

Akiko Okifuji, Gary W. Donaldson, Lynn Barck, and Perry G. Fine

Fibromyalgia syndrome is a prevalent and disabling chronic pain disorder. Past research suggests that obesity is a common comorbidity and may be related to severity. The relationships between the condition and obesity were evaluated. Results suggest that obesity is associated with greater pain sensitivity, poorer sleep quality, and reduced physical strength and flexibility among patients with fibromyalgia syndrome.

1338

Sex Differences in the Relations of Positive and Negative Daily Events and Fatigue in Adults With Rheumatoid Arthritis

Mary C. Davis, Morris A. Okun, Denise Kruszewski, Alex J. Zautra, and Howard Tennen

Fatigue is a common, disabling symptom for individuals with rheumatoid arthritis. This research examined sex differences in the relations between daily changes in positive and negative interpersonal events and fatigue, and tested positive affect and negative affect as mediators of the associations between changes in interpersonal events and fatigue. Findings may help clinicians target factors that can influence fatigue.

1348

Sustained Nociceptive Mechanical Stimulation of Latent Myofascial Trigger Point Induces Central Sensitization in Healthy Subjects

Yi-Meng Xu, Hong-You Ge, and Lars Arendt-Nielsen

Myofascial trigger points are a common cause of regional myofascial pain syndrome and are manifested in widespread musculoskeletal pain syndromes. A large number of regional and widespread musculoskeletal pain syndromes are found to be associated with widespread central sensitization. The aim of the study was to test whether sustained nociceptive mechanical stimulation of latent myofascial trigger points induces widespread mechanical hyperalgesia.

1356

Mammalian Target of Rapamycin Signaling in the Spinal Cord Is Required for Neuronal Plasticity and Behavioral Hypersensitivity Associated With Neuropathy in the Rat

Curtis O. Asante, Victoria C. Wallace, and Anthony H. Dickenson

Neuropathic pain is a complex disorder that can become chronic and can impair quality of life. Despite an increase in knowledge, more research and treatment options are needed. This report finds that alterations in the activity of spinal mammalian target of rapamycin signaling pathways are crucial to the establishment of spinal neuronal plasticity and behavioral hypersensitivity associated with nerve injury. This provides insight into the molecular mechanisms of pain maintenance and potential for new treatment approaches.

1368

An Educational Strategy for Treating Chronic, Noncancer Pain With Opioids: A Pilot Test

Huda Elhwairis and Christopher B. Reznich

Despite the importance of the topic, pain management curricula for healthcare providers is incomplete. This report discusses a curriculum developed for chronic noncancer pain, taught over 4 units. The authors pilot-tested 1 unit (opioids) to internal medicine residents. Findings show that multiple teaching modalities—including didactic lectures, case discussions, write-ups of management plans, and role-play group activities—are effective methods of teaching medical residents about opioid use for chronic noncancer pain.

1376

Pain Variability in Fibromyalgia Is Related to Activity and Rest: Role of Peripheral Tissue Impulse Input

Roland Staud, Michael E. Robinson, Elizabeth E. Weyl, and Donald D. Price

The effects of exercise on pain are ambiguous in studies of fibromyalgia. Exercise-only studies demonstrated increased pain and hyperalgesia during and after activity, yet some studies that included rest periods resulted in decreased pain and increased function. This work examined the effects of alternating exercise with rest. While muscle activity increased overall pain, short rest periods produced analgesic effects. This report concludes that alternating strenuous exercise with rest periods decreased overall clinical pain, and also decreased mechanical hyperalgesia.

1384 **High-Intensity Extended Swimming Exercise Reduces Pain-Related Behavior in Mice: Involvement of Endogenous Opioids and the Serotonergic System**

Leidiane Mazzardo-Martins, Daniel F. Martins, Rodrigo Marcon, Ubirajara D. dos Santos, Breno Speckhann, Vinícius M. Gadotti, André Roberto Sigwalt, Luiz Guilherme A. Guglielmo, and Adair Roberto Soares Santos

The effects of swimming exercise in a chemical behavioral model of nociception – and the mechanisms involved – were examined. Results suggest that high-intensity extended exercise endogenously controls acute pain by activation of opioidergic and serotonergic pathways, supporting the use of exercise as a non-pharmacological approach for the management of acute pain.

1394 **Psychological and Sensory Predictors of Experimental Thermal Pain: A Multifactorial Model**

Christopher J. Starr, Timothy T. Houle, and Robert C. Coghill

The experience of pain is uniquely personal and varies significantly among individuals. This report presents a way to predict subjects' experimental heat pain sensitivity, using a multifactorial model generated from a combination of sensory and psychological factors. Future application in the studies of clinical pain could improve the quality of care provided for pain patients.

1403 **Topical Nifedipine for the Treatment of Localized Provoked Vulvodynia: A Placebo-Controlled Study**

Jacob Bornstein, Ruba Tuma, Yaniv Farajun, Audrey Azran, and Doron Zarfati

Localized provoked vulvodynia, the primary cause of superficial dyspareunia, is recognized by clinicians and researchers as a multi-factorial condition. This study reports that the topical application of both nifedipine and a placebo resulted in reduced pain. This highlights the need for controlled trials of treatments for vulvodynia, and raises doubt about studies conducted without comparison to a placebo.

1410

Therapeutic Interactive Voice Response (TIVR) to Reduce Analgesic Medication Use for Chronic Pain Management

Magdalena R. Naylor, Shelly Naud, Francis J. Keefe, and John E. Helzer

In recent studies, the authors noted the efficacy of Therapeutic Interactive Voice Response to help reduce pain and relapse into pain behavior following group cognitive behavior therapy. This research considered whether this tool can help reduce the use of opioid and other analgesics among chronic pain patients. Findings show this could help patients decrease pain, improve coping, and diminish the likelihood of opioid dependence.

1420

Fatty Acid Amide Hydrolase and Monoacylglycerol Lipase Inhibitors Produce Anti-Allodynic Effects in Mice Through Distinct Cannabinoid Receptor Mechanisms

Steven G. Kinsey, Jonathan Z. Long, Benjamin F. Cravatt, and Aron H. Lichtman

Data addressing the cannabinoid receptor mechanisms underlying the anti-allodynic actions of endocannabinoid catabolic enzyme inhibitors in the mouse sciatic nerve ligation model is presented. Fatty acid amide hydrolase and monoacylglycerol lipase inhibitors reduced allodynia through distinct cannabinoid receptor mechanisms, results suggest. These enzymes offer potential targets to treat neuropathic pain.

1429

Are There Sex Differences in Affective Modulation of Spinal Nociception and Pain?

Jamie L. Rhudy, Emily J. Bartley, Amy E. Williams, Klanci M. McCabe, Mary C. Chandler, Jennifer L. Russell, and Kara L. Kerr

Evidence suggests that women are more sensitive to experimental and clinical pain, but the mechanisms contributing to these differences are poorly understood. Affective processes are known to play a role in regulating pain signaling and pain experience. This research explored whether sex differences in affective experience contribute to sex differences in pain. Results indicate that in healthy individuals, affective processes may not contribute to sex differences in pain.

1442

Opioids, Chronic Pain, and Addiction in Primary Care

Declan T. Barry, Kevin S. Irwin, Emlyn S. Jones, William C. Becker, Jeanette M. Tetrault, Lynn E. Sullivan, Helena Hansen, Patrick G. O'Connor, Richard S. Schottenfeld, and David A. Fiellin

Research has largely ignored the systematic examination of physicians' attitudes toward providing care for patients with chronic non-cancer pain. Perceived barriers to treating patients with chronic non-cancer pain are common among office-based physicians, the authors report. Addressing these barriers in physician training and in existing office-based programs may benefit both non-cancer pain patients and their medical providers.

1451

Comparative Prospective Evaluation of the Responsiveness of Single-Item Pediatric Pain-Intensity Self-Report Scales and Their Uniqueness From Negative Affect in a Hospital Setting

Mark Connelly and Kathleen Neville

Evaluating pain in verbal children in the hospital setting is done primarily through serial assessments of pain intensity using single item measures. Little is known about intensity scales' relative responsiveness and uniqueness from negative affect in this setting. This research compares the responsiveness over time and association with negative affect of 3 single-item pediatric pain intensity scales. The results can help inform the selection of self-report measures when serially evaluating pain.

1461

Corticotropin-Releasing Factor in the Rat Amygdala Differentially Influences Sensory-Discriminative and Emotional-like Pain Response in Peripheral Neuropathy

Nora Bourbia, Osei B. Ansah, and Antti Pertovaara

The central nucleus of the amygdala is involved in the processing and regulation of pain. This report determined whether amygdaloid corticotropin-releasing factor contributes to pain modulation in the neuropathic rat. Conclusions show that corticotropin-releasing factor in the amygdala may have differential effects on sensory and emotional aspects of neuropathic pain.

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