Central sensitization and TMJ abstracts

1. J Pain. 2014 Sep;15(9):956-66. doi: 10.1016/j.jpain.2014.06.008. Epub 2014 Jun 26.

A clinically relevant animal model of temporomandibular disorder and irritable bowel syndrome comorbidity.

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Temporomandibular disorder and irritable bowel syndrome are comorbid functional chronic pain disorders of unknown etiology that are triggered/exacerbated by stress. Here we present baseline phenotypic characterization of a novel animal model to gain insight into the underlying mechanisms that contribute to such comorbid pain conditions. In this model, chronic visceral hypersensitivity, a defining symptom of irritable bowel syndrome, is dependent on 3 factors: estradiol, existing chronic somatic pain, and stress. In ovariectomized rats, estradiol replacement followed by craniofacial muscle injury and stress induced visceral hypersensitivity that persisted for months. Omission of any 1 factor resulted in a transient (1 week) visceral hypersensitivity from stress alone or no hypersensitivity (no inflammation or estradiol). Maintenance of visceral hypersensitivity was estradiol dependent, resolving when estradiol replacement ceased. Referred cutaneous hypersensitivity was concurrent with visceral hypersensitivity. Increased spinal Fos expression suggests induction of central sensitization. These data demonstrate the development and maintenance of visceral hypersensitivity in estradiol-replaced animals following distal somatic injury and stress that mimics some characteristics reported in patients with temporomandibular disorder and comorbid irritable bowel syndrome. This new animal model is a powerful experimental tool that can be employed to gain further mechanistic insight into overlapping pain conditions.PERSPECTIVE: The majority of patients with temporomandibular disorder report symptoms consistent with irritable bowel syndrome. Stress and female prevalence are common to both conditions. In a new experimental paradigm in ovariectomized rats with estradiol replacement, masseter inflammation followed by stress induces visceral hypersensitivity that persists for months, modeling these comorbid pain conditions.

PMCID: PMC4158438
PMID: 24981128 [PubMed - indexed for MEDLINE]

2. Pain Pract. 2013 Nov;13(8):604-13. doi: 10.1111/papr.12029. Epub 2013 Jan 22.

The prevalence of comorbid symptoms of central sensitization syndrome among three different groups of temporomandibular disorder patients.

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AIMS: Symptoms of central sensitization syndrome (CSS) were evaluated among three different groups of temporomandibular disorder (TMD) patients. Additionally, TMD group differences in pain and pain-related disability were assessed, as well as emotional distress.
METHODS: Participants were 250 patients with symptoms of acute TMD, recruited from dental clinics within a major metropolitan area. Sequential regressions and multivariate analyses of covariance were conducted in order to make group comparisons.
RESULTS: Those with a TMD Muscle Disorder (ie, myofacial TMD [m-TMD]) and those with more than one TMD diagnosis had the most symptoms of CSS and higher reports of pain and pain-related disability. Moreover, emotional distress accounted for a substantial amount of the variance for physical symptoms and mediated all TMD comparisons.
CONCLUSIONS: Myofacial TMD is characterized by a high degree of comorbidity of symptoms of CSS and associated emotional distress.

PMCID: PMC3634891
PMID: 23336585 [PubMed - indexed for MEDLINE]

3. Mol Pain. 2011 Dec 6;7:94. doi: 10.1186/1744-8069-7-94.

Calcitonin gene-related peptide promotes cellular changes in trigeminal neurons and glia implicated in peripheral and central sensitization.

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BACKGROUND: Calcitonin gene-related peptide (CGRP), a neuropeptide released from trigeminal nerves, is implicated in the underlying pathology of temporomandibular joint disorder (TMD). Elevated levels of CGRP in the joint capsule correlate with inflammation and pain. CGRP mediates neurogenic inflammation in peripheral tissues by increasing blood flow, recruiting immune cells, and activating sensory neurons. The goal of this study was to investigate the capability of CGRP to promote peripheral and central sensitization in a model of TMD.
RESULTS: Temporal changes in protein expression in trigeminal ganglia and spinal trigeminal nucleus were determined by immunohistochemistry following injection of CGRP in the temporomandibular joint (TMJ) capsule of male Sprague-Dawley rats. CGRP stimulated expression of the active forms of the MAP kinases p38 and ERK, and PKA in trigeminal ganglia at 2 and 24 hours. CGRP also caused a sustained increase in the expression of c-Fos neurons in the spinal trigeminal nucleus. In contrast, levels of P2X3 in spinal neurons were only significantly elevated at 2 hours in response to CGRP. In addition, CGRP stimulated expression of GFAP in astrocytes and OX-42 in microglia at 2 and 24 hours post injection.
CONCLUSIONS: Our results demonstrate that an elevated level of CGRP in the joint, which is associated with TMD, stimulate neuronal and glial expression of proteins implicated in the development of peripheral and central sensitization. Based on

our findings, we propose that inhibition of CGRP-mediated activation of trigeminal neurons and glial cells with selective non-peptide CGRP receptor antagonists would be beneficial in the treatment of TMD.

PMCID: PMC3267674
PMID: 22145886 [PubMed - indexed for MEDLINE]

4. Pain Manag Nurs. 2011 Mar;12(1):15-24. doi: 10.1016/j.pmn.2009.10.003. Epub 2009 Dec 2.

Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders.

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The aim of this study was to review emerging data from the fields of nursing, rheumatology, dentistry, gastroenterology, gynecology, neurology, and orthopedics that support or dispute pathophysiologic similarities in pain syndromes studied by each specialty. A literature search was performed through PubMed and Ovid using the terms fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, irritable bladder/interstitial cystitis, headache, chronic low back pain, chronic neck pain, functional syndromes, and somatization. Each term was linked with pathophysiology and/or central sensitization. This paper presents a review of relevant articles with a specific goal of identifying pathophysiologic findings related to nociceptive processing. The extant literature presents considerable overlap in the pathophysiology of these diagnoses. Given the psychosomatic lens through which many of these disorders are viewed, demonstration of evidence-based links supporting shared pathophysiology between these disorders could provide direction to clinicians and researchers working to treat these diagnoses. "Central sensitivity syndromes" denotes an emerging nomenclature that could be embraced by researchers investigating each of these disorders. Moreover, a shared paradigm would be useful in promoting cross-fertilization between researchers. Scientists and clinicians could most effectively forward the understanding and treatment of fibromyalgia and other common chronic pain disorders through an appreciation of their shared pathophysiology.

PMCID: PMC3052797
PMID: 21349445 [PubMed - indexed for MEDLINE]

5. Mol Pain. 2010 Dec 10;6:89. doi: 10.1186/1744-8069-6-89.

Temporomandibular joint inflammation activates glial and immune cells in both the trigeminal ganglia and in the spinal trigeminal nucleus.

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BACKGROUND: Glial cells have been shown to directly participate to the genesis and maintenance of chronic pain in both the sensory ganglia and the central

nervous system (CNS). Indeed, glial cell activation has been reported in both the dorsal root ganglia and the spinal cord following injury or inflammation of the sciatic nerve, but no data are currently available in animal models of trigeminal sensitization. Therefore, in the present study, we evaluated glial cell activation in the trigeminal-spinal system following injection of the Complete Freund's Adjuvant (CFA) into the temporomandibular joint, which generates inflammatory pain and trigeminal hypersensitivity.
RESULTS: CFA-injected animals showed ipsilateral mechanical allodynia and temporomandibular joint edema, accompanied in the trigeminal ganglion by a strong increase in the number of GFAP-positive satellite glial cells encircling neurons and by the activation of resident macrophages. Seventy-two hours after CFA injection, activated microglial cells were observed in the ipsilateral trigeminal subnucleus caudalis and in the cervical dorsal horn, with a significant up-regulation of Iba1 immunoreactivity, but no signs of reactive astrogliosis were detected in the same areas. Since the purinergic system has been implicated in the activation of microglial cells during neuropathic pain, we have also evaluated the expression of the microglial-specific P2Y12 receptor subtype. No upregulation of this receptor was detected following induction of TMJ inflammation, suggesting that any possible role of P2Y12 in this paradigm of inflammatory pain does not involve changes in receptor expression.
CONCLUSIONS: Our data indicate that specific glial cell populations become activated in both the trigeminal ganglia and the CNS following induction of temporomandibular joint inflammation, and suggest that they might represent innovative targets for controlling pain during trigeminal nerve sensitization.

PMCID: PMC3017032
PMID: 21143950 [PubMed - indexed for MEDLINE]

6. Pain. 2011 Mar;152(3 Suppl):S2-15. doi: 10.1016/j.pain.2010.09.030. Epub 2010 Oct 18.

Central sensitization: implications for the diagnosis and treatment of pain.

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Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, the phenomenon of central sensitization. Central sensitization manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. It can be readily and rapidly elicited in human volunteers by diverse experimental noxious conditioning stimuli to skin, muscles or viscera, and in addition to producing pain hypersensitivity, results in secondary changes in brain activity that can be detected by electrophysiological or imaging techniques. Studies in clinical cohorts reveal changes in pain sensitivity that have been interpreted as revealing an important contribution of central sensitization to the pain phenotype in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and post-surgical pain. The comorbidity of those pain hypersensitivity syndromes that present in the absence of inflammation or a neural lesion, their similar pattern of clinical presentation and response to centrally acting analgesics, may reflect a commonality of central sensitization to their pathophysiology. An important question that still needs to be determined is whether there are individuals with a higher inherited propensity for developing central sensitization than others, and if so, whether this conveys an increased

risk in both developing conditions with pain hypersensitivity, and their chronification. Diagnostic criteria to establish the presence of central sensitization in patients will greatly assist the phenotyping of patients for choosing treatments that produce analgesia by normalizing hyperexcitable central neural activity. We have certainly come a long way since the first discovery of activity-dependent synaptic plasticity in the spinal cord and the revelation that it occurs and produces pain hypersensitivity in patients. Nevertheless, discovering the genetic and environmental contributors to and objective biomarkers of central sensitization will be highly beneficial, as will additional treatment options to prevent or reduce this prevalent and promiscuous form of pain plasticity.

PMCID: PMC3268359
PMID: 20961685 [PubMed - indexed for MEDLINE]

7. J Pain. 2010 Dec;11(12):1295-304. doi: 10.1016/j.jpain.2010.03.005. Epub 2010 May 21.

Referred pain from muscle trigger points in the masticatory and neck-shoulder musculature in women with temporomandibular disoders.

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Our aim was to describe the referred pain patterns and size of areas of trigger points (TrPs) in the masticatory and neck-shoulder muscles of women with myofascial temporomandibular disorders (TMD). Twenty-five women with myofascial TMD and 25 healthy matched women participated. Bilateral temporalis, deep masseter, superficial masseter, sternocleidomastoid, upper trapezius and suboccipital muscles were examined for TrPs by an assessor blinded to the subjects' condition. TrPs were identified with manual palpation and categorized into active and latent according to proposed criteria. The referred pain areas were drawn on anatomical maps, digitalized, and measured. The occurrence of active ($P < .001$) and latent TrPs ($P = .04$) were different between groups. In all muscles, there were significantly more active and latent TrP in patients than controls ($P < .001$). Significant differences in referred pain areas between groups ($P < .001$) and muscles ($P < .001$) were found: the referred pain areas were larger in patients ($P < .001$), and the referred pain area elicited by suboccipital TrPs was greater than the referred pain from other TrPs ($P < .001$). Referred pain areas from neck TrPs were greater than the pain areas from masticatory muscle TrPs ($P < .01$). Referred pain areas of masticatory TrPs were not different ($P > .703$). The local and referred pain elicited from active TrPs in the masticatory and neck-shoulder muscles shared similar pain pattern as spontaneous TMD, which supports the concept of peripheral and central sensitization mechanisms in myofascial TMD.PERSPECTIVE: The current study showed the existence of multiple active muscle TrPs in the masticatory and neck-shoulder muscles in women with myofascial TMD pain. The local and referred pain elicited from active TrPs reproduced pain complaints in these patients. Further, referred pain areas were larger in TMD pain patients than in healthy controls. The results are also in accordance with the notion of peripheral and central sensitization mechanisms in patients with myofascial TMD.

PMID: 20494623 [PubMed - indexed for MEDLINE]

8. J Pain. 2009 Nov;10(11):1170-8. doi: 10.1016/j.jpain.2009.04.017. Epub 2009 Jul 9.

Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing.

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Our aim was to investigate bilateral, widespread pressure-pain hypersensitivity in nerve, muscle, and joint tissues in women with myofascial temporomandibular disorders (TMD) without concomitant comorbid conditions. Twenty women with myofascial TMD (aged 20 to 28 years old), and 20 healthy matched women (aged 20 to 29 years), were recruited. Pressure-pain thresholds (PPT) were bilaterally assessed over supra-orbital (V1), infra-orbital (V2), mental (V3) nerves, median (C5), radial (C6) and ulnar (C7) nerve trunks, the C5-C6 zygapophyseal joint, the lateral pole of the temporo mandibular joint (TMJ), and the tibialis anterior muscle in a blinded design. The results showed that PPTs were significantly decreased bilaterally over the supra-orbital, infra-orbital, and mental nerves, median, ulnar, and radial nerve trunks, the lateral pole of the TMJ, the C5-C6 zygapophyseal joint, and the tibialis anterior muscle in patients with myofascial TMD as compared to healthy controls (all sites: $P < .001$). There were no significant differences in the magnitude of PPT decreases between the trigeminal and extratrigeminal test sites. PPT over the mental nerve, the TMJ, C5-C6 zygapophyseal joint and tibialis anterior muscle were negatively correlated to both duration of pain symptoms and TMD pain intensity ($P < .05$). Our findings revealed bilateral, widespread pressure hypersensitivity in women presenting with myofascial TMD, suggesting that widespread central sensitization is involved in myofascial TMD women.PERSPECTIVE: This article reveals the presence of bilateral and widespread pressure-pain hypersensitivity in women with myofascial TMD, suggesting that widespread central sensitization is involved in myofascial TMD. This finding has implications for development of management strategies.

PMID: 19592309 [PubMed - indexed for MEDLINE]