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CHRONIC PAIN (R STAUD, SECTION EDITOR)

Myofascial Trigger Points: Peripheral or Central Phenomenon?

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Abstract Trigger points (TrP) are hyperirritable spots in a taut band of a skeletal muscle, which usually have referred pain. There is controversy over whether TrP are a peripheral or central nervous system phenomenon. Referred pain, the most characteristic sign of TrP, is a central phenomenon initiated and activated by peripheral sensitization, whereby the peripheral nociceptive input from the muscle can sensitize dorsal horn neurons that were previously silent. TrP are a peripheral source of nociception, and act as ongoing nociceptive stimuli contributing to pain propagation and widespread pain. Several studies support the hypothesis that TrP can induce central sensitization, and appropriate TrP treatment reduces central sensitization. In contrast, preliminary evidence suggests that central sensitization can also promote TrP activity, although further studies are needed. Proper TrP management may prevent and reverse the development of pain propagation in chronic pain conditions, because inactivation of TrP attenuates central sensitization.

Keywords Trigger points · Referred pain · Sensitization · Central · Peripheral · Myofascial · Nociception

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Introduction

Myofascial trigger points (TrP) are one of the most overlooked and ignored causes of musculoskeletal pain. There is evidence suggesting that TrP are a common primary dysfunction and not necessarily secondary to other diagnoses [1]. In other words, TrP may occur in the absence of any underlying medical condition and can constitute an independent cause of pain. TrP can, however, also be co-morbid with a variety of medical musculoskeletal conditions, including osteoarthritis of the hip or knee [2], or with visceral conditions, for example endometriosis [3], interstitial cystitis [4], irritable bowel syndrome, dysmenorrhea, or prostatitis [5].

The most commonly accepted definition describes a TrP as a hyperirritable spot in a taut band of a skeletal muscle, which is painful on compression, stretch, overload, or contraction of the muscle and usually has a distinct referred pain pattern [6]. Clinically, we can distinguish active and latent TrP. The local and referred pain from active TrP reproduces symptoms suffered by patients, who identify the pain as their usual or familiar pain. There is evidence that the local and referred pain from active TrP reproduces the sensory symptoms of individuals with idiopathic neck pain [7], lateral epicondylalgia [8], chronic tension-type headache [9], shoulder pain [10, 11], and

temporomandibular pain [12]. In contrast, the local and referred pain from latent TrP may not reproduce any symptom familiar or usual to the patient [6].

Although latent TrP do not induce spontaneous pain, they can provoke motor dysfunction, e.g. muscle weakness, inhibition, increased motor irritability [13], muscle cramps [14], and altered motor recruitment [15]. During the past decade, an increasing number of researchers have shown an interest in the etiology and clinical relevance of latent TrP [16••].

Development or activation of TrP can result from a variety of factors, including repetitive muscle overuse, acute muscle overload, repetitive minor muscle trauma, psychological stress, and visceral disorders [17]. TrP are located within discrete bands of contractured muscle fibers called taut bands. A taut band signifies a contracture arising endogenously within a limited number of muscle fibers, but not involving the entire muscle [6]. Studies have observed that taut bands have higher stiffness [18], reduced vibration amplitude [19], higher peak systolic velocities, and negative diastolic velocities [20] compared with normal muscle sites. Although different theories have been proposed, the integrated hypothesis is the most accepted model for explaining the pathophysiology of muscle TrP [21•]. In summary, the integrated hypothesis proposes that abnormal depolarization of the post-junctional membrane of motor endplates causes a localized hypoxic energy crisis associated with sensory and autonomic reflex arcs that are sustained by complex sensitization mechanisms. The presence of spontaneous electrical activity or endplate noise, and the clinical evidence that treating TrP eliminates or significantly reduces this endplate noise, support the notion that TrP are located in close proximity to dysfunctional motor endplates [22]. A recent study reported that TrP in the upper trapezius muscle are located in well-defined areas proximal to innervation muscle zones [23]. Although current evidence supports the hypothesis that TrP are associated with dysfunctional motor endplates, the function of muscle spindles in the etiology of TrP has been also investigated [24–26].

The integrated hypothesis postulates that the origin of TrP is a primary dysfunction of the motor endplate. A more recent hypothesis suggests that TrP are caused by a nociception-induced central nervous system disorder, which is centrally maintained by α-motoneuron plateau depolarization, but experimental evidence for this hypothesis is lacking [27].

Recently, several researchers have investigated a possible relationship between TrP and sensitization mechanisms [28••]. TrP may be a cause of central sensitization, but it is also conceivable that TrP are the result of central sensitization; in other words, are TrP a peripheral or a central phenomenon? This paper will discuss different sensory aspects of TrP, whereby both peripheral and central sensitization mechanisms are involved simultaneously, and briefly address clinical implications.

Muscle Referred Pain: Peripheral or Central Phenomenon?

One of the characteristic signs of TrP is the presence of referred pain. Pain felt at the source of pain is termed "local pain" or "primary pain," whereas pain felt in a region away from the source of pain is termed "referred pain." Referred pain can be perceived in any region of the body, but the size of the referred pain area is variable and at least partially affected by pain-induced changes to central somatosensory maps. Because the intensity of referred pain and the size of the referred pain area are positively correlated with central nervous system excitability, it is now generally assumed that muscle referred pain is a central sensitization process mediated by a peripheral sensitization phenomenon, with additional sympathetic activity facilitation and dysfunctional descending pain inhibition [29, 30].

Among the different theories explaining the neurophysiology of referred pain, the central hyper-excitability theory explains the principal characteristics of referred pain in most detail. According to this theory, referred pain occurs at the dorsal horn level and is the result of activation, by means of sensitization mechanisms, of quiescent axonal connections between affective nerve fibers' dorsal horn neurons [1]. Hoheisel et al. reported that new receptive fields emerged within minutes after experience of noxious stimuli [31], explaining the delay between the noxious input and development of referred pain [32]. In clinical practice referred pain appears within seconds of stimulation of a TrP, suggesting that induction of these axonal changes is a rapid process. TrP are more effective than non-TrP regions at inducing neuroplastic changes in the dorsal horn neurons [33].

These findings support the hypothesis that referred pain elicited by TrP is a central phenomenon initiated, activated, and maintained by peripheral sensitization. Peripheral nociceptive input can sensitize previously silent dorsal horn neurons. Because anesthetization of the referred pain area reduces pain, it would seem that peripheral processes contribute to referred pain [34].

However, it is also clear that central sensitization processes are involved in the development of spreading pain, because larger referred pain areas in patients with chronic pain are a consequence of higher central neural plasticity [35]. Maintenance of referred pain is dependent on ongoing nociceptive input from the site of primary muscle pain [29]. There is currently insufficient data to determine which sensitization mechanism, peripheral or central, is more relevant to the development of referred pain.

Trigger Points: A Peripheral Source of Nociception

Peripheral sensitization is described as a reduction in the pain threshold and an increase in responsiveness of the peripheral

nociceptors. Muscle pain is associated with the activation of muscular nociceptors by a variety of endogenous substances, including neuropeptides and inflammatory mediators [1]. Studies conducted by Shah et al. revealed that the concentrations of bradykinin (BK), calcitonin gene-related peptide (CGRP), substance P, tumor necrosis factor-α (TNF-α), interleukins 1β, IL-6, and IL-8, serotonin (5-HT), and norepinephrine were significantly higher at active TrP than at latent TrP or non-TrP points [36]. Interestingly, concentrations of the same biochemical and algogenic substances in a pain-free area of the gastrocnemius muscle were also higher for subjects with active TrP in the upper trapezius muscle compared with subjects with latent TrP or non-TrP points [37]. More recently, Hsieh et al. confirmed the presence of multiple biochemical substances in the immediate proximity of TrP [38••]. Both the studies by Shah et al. [36, 37] and Hsieh et al. [38••] provided evidence that therapeutic intervention with dry needling could modulate and normalize the chemical environment of TrP, supporting the theory that TrP may be a source of peripheral nociceptive input.

Li et al. observed nociceptive (hyperalgesia) and non-nociceptive (allodynia) hypersensitivity at TrP, suggesting that TrP sensitize nociceptive and non-nociceptive nerve endings [39]. Wang et al. reported that blocking large-diameter myelinated muscle afferents increased pressure pain and referred pain thresholds at TrP, but not at non-TrP regions, suggesting that non-nociceptive large-diameter myelinated muscle afferents are also involved in TrP pain [40]. These studies establish the presence of nociceptive pain hypersensitivity at TrP and confirm that TrP are a focus of peripheral sensitization.

Myofascial TrP can act as ongoing nociceptive stimuli contributing to spatial pain propagation and widespread pain, as confirmed by a study in which painful stimulation of latent TrP in asymptomatic subjects induced early occurrence of a locally enlarged area of pressure hyperalgesia and central sensitization [41].

Trigger Points can Induce Central Sensitization

Emerging research suggests a physiological link between the clinical manifestations of TrP, e.g. hyperalgesia, allodynia, and referred pain, and central sensitization, although the causal mechanisms are still unclear. Mense suggested that, because TrP constitute a continued peripheral nociceptive afferent barrage into the central nervous system, the presence of multiple TrP in the same or different muscles or the presence of TrP for prolonged periods of time can sensitize spinal cord neurons and supra-spinal structures [42].

A relationship between active TrP and central sensitization has been suggested for many years, but it was not until the past decade that neuro-physiological studies were initiated. Kuan et al. observed that spinal cord connections of TrP were more effective than non-TrP tissue at inducing neuroplastic changes in the dorsal horn neurons, and were connected to a greater number of small sensory or nociceptive neurons [33]. Xu et al. reported that painful stimulation of latent TrP induced central sensitization in healthy subjects, because stimulation of TrP increased pressure hypersensitivity of extra-segmental tissues [43]. A few studies observed that stimulation of TrP induced enhanced activity of brain areas including the primary and secondary somatosensory cortex, the inferior parietal cortex, and the mid and anterior insula [44, 45], supporting the hypothesis that TrP can induce central sensitization.

TrP are also a focus of peripheral noxious sensitization, as illustrated by Fernández-de-las-Peñas et al., who formulated a pain model applied to tension-type headache. Peripheral sensitization of muscle nociceptors and central sensitization both seem to be linked to active TrP located in muscles innervated by the upper cervical nerve roots and the trigeminal nerve. TrP may be responsible for peripheral nociception and produce a continuous afferent barrage into the trigeminal nerve nucleus caudalis, hence sensitizing the central nervous system [46]. Further support for the hypothesis that TrP may induce central sensitization can be derived from the observation that proper management of TrP can reduce central sensitization. There is evidence that central sensitization is a reversible process in individuals with TrP [35], although traditionally central sensitization has been believed an irreversible process, at least in animals [47]. Injections into TrP of neck muscles produced rapid relief of palpable scalp and facial tenderness and associated symptoms of migraine [48]. Anesthetic injections into active TrP significantly reduced mechanical hyperalgesia, allodynia, and referred pain for individuals with migraine [49], fibromyalgia [50], and whiplash [51].

The cause of the rapid decrease in local and referred pain associated with TrP therapy, observed in clinical practice, is not fully understood. The resolution of TrP-associated referred pain is related to the decrease of nociceptive input to dorsal horn neurons of the spinal cord, and to interruption of the spread of pain and central sensitization. The reversal of referred pain is fast, suggesting that central sensitization can indeed be reversed with proper treatment. A recent study supported the hypothesis that altered pain processing seems to be driven by peripheral noxious stimuli. The researchers described normalization of widespread pressure-pain hyperalgesia after successful hip replacement in subjects with symptomatic hip osteoarthritis [52]. Several factors affect central sensitization associated with TrP, including descending inhibitory pathways and sympathetic or neuropathic activity.

Central Sensitization can Promote Trigger Point Activity

Although there is evidence that TrP can initiate central sensitization, there is also some preliminary evidence that central

sensitization can promote TrP activity. It is known that a sensitized central nervous system may modulate referred muscle pain. For example, infusions of the N-methyl-D-aspartate (NMDA) antagonist ketamine reduced referred pain areas in subjects with fibromyalgia [53]. In addition, an increased degree of central sensitization is associated with larger referred pain areas from TrP [1, 9, 29].

The only study suggesting that TrP can result from central sensitization was conducted by Srbely et al. [54], who hypothesized that pain arising from TrP may be caused by neurogenic mechanisms secondary to central sensitization. They postulated that central sensitization may increase TrP sensitivity in segmentally related muscles; however, the study did not establish a cause-and-effect relationship [54]. If central sensitization could cause TrP, it would be reasonable to assume that TrP would not be present in healthy, pain-free subjects where central sensitization mechanisms are not present. There are, however, several studies revealing that asymptomatic healthy subjects also have TrP—because the subjects are pain free, these would be classified as latent TrP, [2, 3, 7–15, 16••, 23, 24, 40, 41, 43]. Latent TrP are not spontaneously painful, but they do provide nociceptive barrage into the dorsal horn [13–15, 16••, 24, 40, 41, 43].

Although there is no evidence supporting the hypothesis that TrP are a result of central sensitization, in clinical practice individuals with higher levels of central sensitization present with multiple TrP.

Implications for Clinical Practice

Current data supports the hypothesis that TrP can affect the development of central sensitization. Because muscle TrP are common in many chronic pain conditions and they initiate, activate, and maintain sensitization of central pathways, it is important to realize that untreated TrP can cause chronic or persistent pain. Therefore, TrP should be treated as soon and as effectively as possible to avoid development of persistent pain. Proper management of TrP may prevent and reverse the development of spatial pain propagation in chronic pain conditions. Inactivation of TrP is associated with attenuation of central sensitization [49–51] and induction of spinal inhibition [55, 56]. Determining the proper treatment approach for each individual patient with chronic or persistent pain is challenging for clinicians, because patients will probably have different clinical presentations. In developing an effective management plan, the manifestations of both peripheral and central sensitization mechanisms of a particular condition or clinical presentation must be included in the decision tree. In other words, clinical management of patients with central sensitization needs to extend beyond tissue-based pathology and incorporate strategies directed at normalizing or reducing central nervous system sensitivity [57].

The treatment plan should include two main components. First, peripheral and central nervous system sensitivity must be targeted by means of appropriate interventions. Second, the descending inhibitory systems must be activated [58]. Inactivating TrP and addressing their perpetuating and promoting factors has an important function in achieving these objectives, because removing the peripheral nociceptive input from TrP will modulate the patient's central sensitivity.

Clinically, when a patient presents with a pain problem mediated by predominantly peripheral sensitization mechanisms, functional activity and early and appropriate treatment of the noxious inputs should be encouraged. This may involve inactivating TrP, and mobilizing joints and nerves. For a patient with a more persistent condition mediated by predominantly central sensitization mechanisms, a multimodal therapy program is the preferred approach, which may include pharmacological and medical management, physical therapy, and cognitive behavioral or psychodynamic therapy. Depending on the chronicity of the disorder and the associated disability, patients should receive pain neuroscience education addressing the neurobiology of pain and pain mechanisms, fear, anxiety, and other psychosocial variables [59]. Patients need to develop different strategies for optimizing normal functional movement and to undertake active and specific or more global exercises, including aerobic exercise.

Conclusions

To determine whether muscle TrP are a peripheral or central phenomenon, multiple lines of research must be considered. Available data supports the hypothesis that TrP are a persistent peripheral source of nociception contributing to pain propagation and widespread pain. The clinical finding that inactivating TrP attenuates central sensitization further supports the hypothesis that TrP are a primarily peripheral phenomenon. As research in this field continues to expand, it is conceivable that central phenomena will be found to contribute to the development of TrP. However, experimental evidence is currently sparse.

Compliance with Ethics Guidelines

Conflict of Interest César Fernández-de-las-Peñas and Jan Dommerholt declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Mense S, Gerwin RD, editors. Muscle pain: understanding the mechanisms. Berlin: Springer-Verlag; 2010.
2. Bajaj P, Bajaj P, Graven-Nielsen T, Arendt-Nielsen L. Trigger points in patients with lower limb osteoarthritis. J Musculoskelet Pain. 2001;9(3):17–33.
3. Jarrell J. Endometriosis and abdominal myofascial pain in adults and adolescents. Curr Pain Headache Rep. 2011;15:368–76.
4. Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency–frequency syndrome. J Urol. 2001;166:2226–31.
5. Doggweiler-Wiygul R. Urologic myofascial pain syndromes. Curr Pain Headache Rep. 2004;8:445–51.
6. Simons DG, Travell JG, Simons LS. Myofascial pain and dysfunction: the trigger point manual, vol. 1. Philadelphia: Lippincott William & Wilkins; 1999.
7. Fernández-de-las-Peñas C, Alonso-Blanco C, Miangolarra JC. Myofascial trigger points in subjects presenting with mechanical neck pain: a blinded, controlled study. Man Ther. 2007;12:29–33.
8. Fernández-Carnero J, Fernández-de-las-Peñas C, de-la-Llave-Rincón AI, Ge HY, Arendt-Nielsen L. Prevalence of and referred pain from myofascial trigger points in the forearm muscles in patients with lateral epicondylalgia. Clin J Pain. 2007;23:353–60.
9. Fernández-de-las-Peñas C, Schoenen J. Chronic tension type headache: what's new? Curr Opin Neurol. 2009;22:254–61.
10. Ge HY, Fernández-de-las-Peñas C, Madeleine P, Arendt-Nielsen L. Topographical mapping and mechanical pain sensitivity of myofascial trigger points in the infraspinatus muscle. Eur J Pain. 2008;12:859–65.
11. Bron C, Dommerholt J, Stegenga B, Wensing M, Oostendorp RA. High prevalence of shoulder girdle muscles with myofascial trigger points in patients with shoulder pain. BMC Musculoskelet Disord. 2011;12:139.
12. Fernández-de-las-Peñas C, Galán-del-Río F, Alonso-Blanco C, Jiménez-García R, Arendt-Nielsen L, Svensson P. Referred pain from muscle trigger points in the masticatory and neck-shoulder musculature in women with temporomandibular disorders. J Pain. 2010;11:1295–304.
13. Ibarra JM, Ge HY, Wang C, Martínez Vizcaíno V, Graven-Nielsen T, Arendt-Nielsen L. Latent myofascial trigger points are associated with an increased antagonistic muscle activity during agonist muscle contraction. J Pain. 2011;12:1282–8.
14. Ge HY, Zhang Y, Boudreau S, Yue SW, Arendt-Nielsen L. Induction of muscle cramps by nociceptive stimulation of latent myofascial trigger points. Exp Brain Res. 2008;187:623–9.
15. Lucas KR, Rich PA, Polus BI. Muscle activation patterns in the scapular positioning muscles during loaded scapular plane elevation: the effects of latent myofascial trigger points. Clin Biomech. 2010;25:765–70.
16. •• Ge HY, Arendt-Nielsen L. Latent myofascial trigger points. Curr Pain Head Rep. 2011;15:386–92. *An updated article supporting the clinical relevance of latent trigger points*.
17. Gerwin RD, Dommerholt J, Shah JP. An expansion of Simons' integrated hypothesis of trigger point formation. Curr Pain Headache Rep. 2004;8:468–75.
18. Chen Q, Bensamoun S, Basford JR, et al. Identification and quantification of myofascial taut bands with magnetic resonance elastography. Arch Phys Med Rehabil. 2007;88:1658–61.
19. Sikdar S, Shah JP, Gilliams E, et al. Novel applications of ultrasound technology to visualize and characterize myofascial trigger points and surrounding soft tissue. Arch Phys Med Rehabil. 2009;90:1829–38.
20. Sikdar S, Ortiz R, Gebreab T, Gerber LH, Shah JP. Understanding the vascular environment of myofascial trigger points using ultrasonic imaging and computational modeling. Conf Proc IEEE Eng Med Biol Soc. 2010;1:5302–5.
21. • Bron C, Dommertholt J. Etiology of myofascial trigger points. Curr Pain Headache Rep. 2012;16:439–44. *An article updating the etiology of muscle trigger points*.
22. Ge HY, Fernández-de-las-Peñas C, Yue SW. Myofascial trigger points: spontaneous electrical activity and its consequences for pain induction and propagation. Chin Med. 2011;6:13.
23. Barbero M, Cescon C, Tettamanti A, Leggero V, Macmillan F, Coutts F, et al. Myofascial trigger points and innervation zone locations in upper trapezius muscles. BMC Musculoskelet Disord. 2013;14:179.
24. Ge HY, Serrao M, Andersen OK, Graven-Nielsen T, Arendt-Nielsen L. Increased H-reflex response induced by intramuscular electrical stimulation of latent myofascial trigger points. Acupunct Med. 2009;27:150–4.
25. Partanen JV. End plate spikes in the human electromyogram. Revision of the fusimotor theory. J Physiol Paris. 1999;93:155–66.
26. Partanen JV, Ojala TA, Arokoski PA. Myofascial syndrome and pain: a neurophysiological approach. Pathophysiology. 2010;17:19–28.
27. Hocking MJL. Exploring the central modulation hypothesis: do ancient memory mechanisms underlie the patho-physiology of trigger points? Curr Pain Headache Rep. 2013;17:347.
28. •• Dommertholt J. Dry needling: peripheral and central considerations. J Manual Manipulative Ther. 2011;19:223–37. *An article suggesting a relationship between sensitization and trigger points*.
29. Arendt-Nielsen L, Svensson P. Referred muscle pain: basic and clinical findings. Clin J Pain. 2001;17:11–9.
30. Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain. 2008;40:465–71.
31. Hoheisel U, Mense S, Simons DG, Yu XM. Appearance of new receptive fields in rat dorsal horn neurons following noxious stimulation of skeletal muscle: a model for referral of muscle pain? Neurosci Lett. 1993;153:9–12.
32. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Quantification of local and referred muscle pain in humans after sequential intra-muscular injections of hypertonic saline. Pain. 1997;69:111–7.
33. Kuan TS, Hong CZ, Chen JT, Chen SM, Chien CH. The spinal cord connections of the myofascial trigger spots. Eur J Pain. 2007;11:624–34.
34. Rubin TK, Gandevia SC, Henderson LA, Macefield VG. Effects of intramuscular anesthesia on the expression of primary and referred pain induced by intramuscular injection of hypertonic saline. J Pain. 2009;10:829–35.
35. Arendt-Nielsen L, Laursen RJ, Drewes AM. Referred pain as an indicator for neural plasticity. Prog Brain Res. 2000;129:343–56.
36. Shah JP, Phillips TM, Danoff JV, Gerber LH. An in-vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. J Appl Physiol. 2005;99:1977–84.
37. Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, et al. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil. 2008;89:16–23.
38. •• Hsieh XL, Yang SA, Yang CC, Chou LW. Dry needling at myofascial trigger spots of rabbit skeletal muscles modulates the biochemicals associated with pain, inflammation, and hypoxia. Evid Based Complement Alternat Med. 2012;2012:342165. *An*

article confirming that trigger points are a peripheral source of nociception.

39. Li LT, Ge HY, Yue SW, Arendt-Nielsen L. Nociceptive and non-nociceptive hypersensitivity at latent myofascial trigger points. Clin J Pain. 2009;25:132–7.
40. Wang YH, Ding X, Zhang Y, et al. Ischemic compression block attenuates mechanical hyperalgesia evoked from latent myofascial trigger point. Exp Brain Res. 2010;202:265–7.
41. Wang C, Ge HY, Ibarra JM, Yue SW, Madeleine P, Arendt-Nielsen L. Spatial pain propagation over time following painful glutamate activation of latent myofascial trigger points in humans. J Pain. 2012;13:537–45.
42. Mense S. Referral of muscle pain. APS J. 1994;3:1–9.
43. Xu YM, Ge HY, Arendt-Nielsen L. Sustained nociceptive mechanical stimulation of latent myofascial trigger point induces central sensitization in healthy subjects. J Pain. 2010;11:1348–55.
44. Niddam DM, Chan RC, Lee SH, Yeh TC, Hsieh J. Central representation of hyperalgesia from myofascial trigger point. Neuroimage. 2008;39:1299–306.
45. Niddam DM. Brain manifestation and modulation of pain from myofascial trigger points. Curr Pain Headache Rep. 2009;13:370–5.
46. Fernández-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Simons DG, Pareja JA. Myofascial trigger points and sensitization: an updated pain model for tension type headache. Cephalalgia. 2007;27:383–93.
47. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve. 2001;24:37–46.
48. Mellick GA, Mellick LB. Regional head and face pain relief following lower cervical intramuscular anesthetic injection. Headache. 2003;43:1109–11.
49. Giamberardino MA, Tafuri E, Savini A, et al. Contribution of myofascial trigger points to migraine symptoms. J Pain. 2007;8:869–78.
50. Affaitati G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino M. Effects of treatment of peripheral pain generators in fibromyalgia patients. Eur J Pain. 2011;15:61–9.
51. Freeman MD, Nystrom A, Centeno C. Chronic whiplash and central sensitization; an evaluation of the role of a myofascial trigger points in pain modulation. J Brachial Plex Peripher Nerve Inj. 2009;4:2.
52. Aranda-Villalobos P, Fernández-de-Las-Peñas C, Navarro-Espigares JL, Hernández-Torres E, Villalobos M, Arendt-Nielsen L, et al. Normalization of widespread pressure pain hypersensitivity after total hip replacement in patients with hip osteoarthritis is associated with clinical and functional improvements. Arthritis Rheum. 2013;65:1262–70.
53. Graven-Nielsen T, Aspegren-Kendall S, Henriksson KG, et al. Ketamine attenuates experimental referred muscle pain and temporal summation in fibromyalgia patients. Pain. 2000;85:483–91.
54. Srbely JZ, Dickey JP, Bent LR, Lee D, Lowerison M. Capsaicin-induced central sensitization evokes segmental increases in trigger point sensitivity in humans. J Pain. 2010;11:636–43.
55. Srbely JZ, Dickey JP, Lowerison M, Edwards AM, Nolet PS, Wong LL. Stimulation of myofascial trigger points with ultrasound induces segmental antinociceptive effects: a randomized controlled study. Pain. 2008;139:260–6.
56. Srbely JZ, Dickey JP, Lee D, Lowerison M. Dry needle stimulation of myofascial trigger points evokes segmental anti-nociceptive effects. J Rehabil Med. 2010;42:463–8.
57. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Man Ther. 2010;15:135–41.
58. Nijs J, Meeus M, Van Oosterwijck J, Roussel N, De Kooning M, Ickmans K, et al. Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have? Expert Opin Pharmacother. 2011;12:1087–98.
59. Puentedura EL, Louw A. A neuroscience approach to managing athletes with low back pain. Phys Ther Sports. 2012;13:123–33.