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Review Article

Preclinical models of deep craniofacial nociception and temporomandibular disorder pain

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ABSTRACT

Chronic pain in temporomandibular disorder (TMD) is a common health problem. Cumulating evidence indicates that the etiology of TMD pain is complex with multifactorial experience that could hamper the developments of treatments. Preclinical research is a resource to understand the mechanism for TMD pain, whereas limitations are present as a disease-specific model. It is difficult to incorporate multiple risk factors associated with the etiology that could increase pain responses into a single animal. This article introduces several rodent models which are often employed in the preclinical studies and discusses their validities for TMD pain after the elucidations of the neural mechanisms based on the clinical reports. First, rodent models were classified into two groups with or without inflammation in the deep craniofacial tissues. Next, the characteristics of each model and the procedures to identify deep craniofacial pain were discussed. Emphasis was directed on the findings of the effects of chronic psychological stress, a major risk factor for chronic pain, on the deep craniofacial nociception. Preclinical models have provided clinically relevant information, which could contribute to better understand the basis for TMD pain, while efforts are still required to bridge the gap between animal and human studies.

1. Introduction

Temporomandibular disorder (TMD) is a group of musculoskeletal conditions that could affect the deep craniofacial tissues such as temporomandibular joint (TMJ) and jaw muscles, and is a major cause of non-odontogenic orofacial pain in dental practice [1–6]. Chronic pain is the common reason for seeking treatment in TMD patients, whereas about 10% of patients required for treatments [2]. TMD symptoms are mild in nature, while some patients will progress to chronic pain, which could interfere with social life activities [7,8]. It is no doubt that alleviation of chronic pain is an important issue to elevate the quality of life [9,10]. Unfortunately, the basis for chronic pain is not fully understood, which could hamper the development of the treatments indicated by several reasons. TMD pain is complex with multifactorial experience encompassing sensory discriminative, emotional, and motivational dimensions [2,4,11,12]. The variety of comorbidities is associated with TMD pain, indicating that a single dimensional treatment is not sufficient to reduce chronic pain. For example, controlling psychological stress could be a crucial to reduce TMD pain [13].

This article reviews two issues. First, the neural mechanisms for TMD pain are discussed based on the clinical and preclinical studies. Emphasis is directed on the discussion of validity and characteristics of preclinical models for TMD [14–17]. Further, the experimental procedures to identify the nociceptive responses in the deep craniofacial tissues are discussed in the preclinical models. Second, the involvements of affective factors in the deep craniofacial nociception are discussed, since psychological distress is one of the critical risk factors that exacerbate TMD pain [2,9,10,12,18].

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2. Neural mechanisms for pain in the deep craniofacial tissues in human

2.1. Neural changes

A general idea underlying pain-related neural change is neuroplasticity, corresponding to the changes in neural structure and function that could explain various pain conditions [14,16,19–21]. Procedures such as quantitative sensory tests and imaging examinations have been employed to understand the pain mechanism.

2.2. Peripheral neural mechanisms (PNS)

Biochemical studies demonstrate the changes in the level of inflammatory mediators, which can sensitize the nociceptors in the deep craniofacial tissues [22–25]. Proinflammatory mediators affect nociception in the deep craniofacial tissues. Cytokines such as interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha are identified in the synovial fluid of the TMJ in TMD patients [25–27], whereas those are not detected in the healthy controls [26]. Painful TMD with disk displacement (DD) without reduction displays higher levels of IL-1 beta, TNF-alpha and TNF-beta in the TMJ compared with that with DD with reduction [27]. TMD patients suffering from osteoarthritis show a higher level of IL-1 beta in synovial fluids [22,26,27]; however, most cytokines except IL-1 beta are less correlated with pain [26]. IL-1 beta has been reported to play critical roles on the development and progression of TMD pain [22,24]. IL-2, -8 and -13 in the blood serum also indicate significant effects on generalized pain in TMD patients [28]. Besides cytokines, several mediators including prostaglandin E2, bradykinin and serotonin (5HT) are detected in the synovial fluid of TMJ in the TMD patients with internal derangements and osteoarthritis of TMJ, however, no correlation is found between each mediator and pain [29].

Myofascial TMD pain patients display changes in the level of inflammatory mediators in the masseter muscle [22]. For example, the levels of cytokines including IL-6, 7, 8 and 13 are elevated in the masseter muscle; however, there is no direct cause-relation between pain and cytokine levels [30]. Myofascial TMD patients also display elevated concentration of glutamate in the masseter muscle compared to healthy controls after the masseter muscle injection of glutamate [31]. The level of 5HT in the masseter muscle evoked by hypertonic saline injection is increased in healthy controls [32], while myogenic TMD pain patients show higher 5HT levels in the masseter muscle by the acute injury compared to healthy controls [33]. Further, increases in antioxidative stress markers in the saliva, resulting from inflammatory processing, are identified in myogenous TMD patients; however, no correlation is seen between pain and the level of oxidative markers [34].

Quantitative sensory tests demonstrate the underlying neural mechanisms in the PNS. Because of the presence of inflammatory mediators in the deep craniofacial tissues, effects of those mediators on nociception have been determined in healthy controls and TMD patients. For example, local injection of cytokines [30], glutamate [35–38], serotonin [39], acid saline [40] and nerve growth factor [41,42] can cause pain and hyperalgesia in the deep craniofacial tissues. These results are consistent with the findings that TMD patients increase experimentally-induced pain sensitivity in the facial areas, in which the level of inflammatory mediators is elevated [24,27–33,43,44].

Analgesic efficacy of local administration of the specific receptor-related agonists and/or antagonists could determine the neural mechanisms in the PNS, indirectly. For example, glutamate injection of the TMJ region causes hyperalgesia in the facial region, which is inhibited by blockade of the *N*-methyl-D-aspartate (NMDA) receptors in the TMJ region [35]. However, blockade of local NMDA receptors could not decrease masseter muscle pain and hyperalgesia evoked by the injection of hypertonic saline into the masseter muscle [45]. Hyperalgesia in the masseter muscle is reduced by blockade of 5HT3 receptors in the masseter muscle of TMD patients with a higher density of 5HT3 receptors in the masseter muscle compared to healthy controls [46,47]. TMJ or masseter muscle injection of opioids decreases hyperalgesia evoked by mechanical stimulation to the face in painful TMD [48,49], whereas intra-TMJ capsule injection of lidocaine shows less reduction of the jaw opening pain with disc displacement without reduction [50]. Neuroimaging technology enables visualization of structural changes in the nervous system associated with nociception [23,51]. Further, the magnetic resonance imaging (MRI) demonstrates that painful TMD patients show neural degeneration of the trigeminal nerves [20,52]. However, there are minor cause-relations between structural changes in the trigeminal nerve and pain conditions [52]. These findings, collectively, indicate that neural changes in PNS could be involved in TMD pain; however, changes in the PNS mechanism alone cannot explain the basis for TMD pain due to several contradicting results shown above.

2.3. Central neural mechanisms (CNS)

Neural changes in the CNS play critical roles on TMD pain [6,14,19,21,53–55]. Painful TMD displays less tissue injury in the deep craniofacial tissues, while the correlation of elevated inflammatory mediators with chronic pain is inconsistent [22–24,26]. TMD pain could be associated with comorbid negative psychology and disturbances in the body [14,16,18]. TMD patients often show pain in multiple body areas [43,54,56]. Further, TMD myogenic [44] and arthralgia [57] patients have greater sensitivities to experimental pain responses within and/or outside the craniofacial areas [43,54].

Several procedures can assess the dysfunction of descending pain control clinically, which could be implicated as the CNS roles on chronic pain [55]. First, enhanced temporal summation of pain (TSP) could allow to assess the dysfunction of the CNS, indicated by pain facilitation. In brief, to measure pain facilitation by TSP, a noxious stimulation was given repeatedly at a certain frequency to induce pain summation, which could be correlated to the wind-up phenomenon. Painful TMD patients show facilitated TSP to noxious stimuli applied to the trigeminal and extra-trigeminal regions [56,58,59]. Second, the assessment of conditioned pain modulation (CPM) reveals the impaired descending pain inhibitory systems [6]. CPM refers to the inhibition of pain response evoked by a tested stimulation due to the interference of a second stimulation applied to a remote area, simultaneously or sequentially. Despite contradicting results being reported [55,56], TMD patients display reduced CPM responses [60,61]. Further, evidence suggests that CPM response in the trigeminal-innervated body regions is weaker compared with those in the extra-trigeminal innervated areas [62]. Third, transcutaneous electric nerve stimulation (TENS) has been suggested to manage TMD pain on the mechanisms of the resulting pain relief through the CNS mechanisms [63–65]. The basis for inhibitory effects of TENS on TMD pain is not fully understood, but the modulatory roles of TENS on descending pain controls in the CNS are considered [21,66]. Interestingly, the effects of TENS on neural functions, particularly autonomic functions, could be altered under chronic pain conditions, since TMD patients exhibited different pattern of the pupil reaction by TENS compared with healthy controls [67]. Fourth, neuroimaging studies have revealed the findings of abnormalities in the higher level of the CNS related to pain, emotion, and motor functions in TMD patients [20,22,23,53,68]. For example, TMD patients display a cortical thickening in the cortex [69], increases in gray matter volume in the thalamus [70] and increases in functional connectivity between insular cortex

and anterior cingulate cortex [71]. Besides the higher CNS areas, structural changes are demonstrated in the lower CNS areas including the brainstem in TMD patients [52,70]. For example, the gray matter volume is decreased in the raphe magnus nucleus (NRM) and medullary dorsal horn, while the mean diffusivity is increased in those areas in TMD pain [52]. Similar findings are observed in headache and visceral pain patients [72,73].

2.4. Risk factors for TMD pain

Several risk factors contribute to the onset of TMD pain, and consequently controlling risk factors for TMD could be the initial step toward the alleviation of pain [2,74–77]. In this section, the overview of the psychological stress effects on the deep craniofacial nociception is discussed, and emphasis is placed on the elucidation of preclinical models for psychological stress conditions.

The greater prevalence of females in TMD patients cannot be ignored to discuss the basis for TMD pain [43,78,79]. Evidence has demonstrated the sex differences in the deep craniofacial nociception [37,80–82]. The underlying mechanisms of sex differences in TMD pain have been investigated in the preclinical studies from the point of changes in the level of sex hormones, and several hormones such as estrogen [83–85], progesterone [86,87] and testosterone [88] play roles. In this article, we will not discuss this issue, which is described elsewhere [89–91].

2.5. Psychological stress in TMD patients

A high incidence of exposure to stressful life events has been reported in TMD patients [12]. TMD patients display high levels of depression and anxiety [18]. Perceived stress and depression are associated with the prediction of TMD pain and psychological stress is associated with widespread pain in TMD patients [92,93]. A recent cohort study demonstrates that COVID-19 pandemic-related psychosocial stress conditions enhanced chronic pain in TMD patients [94]. These reports indicate that psychological stress could be involved in the onset and maintenance of chronic pain, while the alleviation of TMD pain by behavioral treatments and medication using antidepressants indicates that dysfunction of CNS could play roles on the mediation of painful TMD [95]. In Section 4, the effects of psychological stress on the deep craniofacial nociception using preclinical models are discussed.

3. Neural mechanisms for pain in the deep craniofacial tissues in animals

Pain research to investigate its mechanism has shown significant progress with the establishments of preclinical models [14–17,96–98]. In particular, behavioral alterations of nociception have been key indicators for the investigation of the similarity between animals and human pain. In the following sections, we introduce various preclinical models for TMD pain often used, and discuss the characters of the models with the strength and limitations. Further, emphasis is placed in the discussion on the similarities of the features in preclinical models with those in TMD patients [6,14,20,22,99–101].

3.1. Pain in the deep craniofacial tissues in the preclinical models (Table 1)

As TMD pain is multidimensional experiences, preclinical models need to possess such characters. It is, however, difficult to incorporate those into a single animal model [15–17]. Researchers have often picked one or two risk factors like local injury (e.g. inflammation), psychological stress and different levels of hormones. Then, effects of the risk factor that we built in the animals artificially have been determined on nociception in the deep craniofacial tissues [6,14,15,17,90,96].

Table 1
Preclinical models mimicking TMD pain conditions shown in this article.

1. Local inflammatory model[a]	2. Non-local inflammatory model
• CFA	A Oral function model
• Formalin	• Jaw opening
• Mustard oil	• Occlusal interference
• Carrageenan	B Jaw muscle pain model
• Capsaicin	• Repeated jaw muscle contraction
• ATP	• Jaw muscle tendon ligation
• Cytokines	C Psychological stress model
• Monosodium iodoacetate	• Chronic restraint
• Nerve growth factor	• Repeated forced swim
	• Social defeat stress
	• Others

[a] Injection of chemicals into the deep craniofacial tissues.

In this article, preclinical models are categorized into either "local inflammatory" or "non-local inflammatory" model. The "local inflammatory" model is defined by the features that inflammation in the deep craniofacial tissues is intentionally evoked by the local administration of various chemical substances. "Non-local inflammatory" model is developed by local manipulations with less invasive intervention or by systemic manipulations such as psychological stress conditionings and hormonal treatments.

3.1.1. Local inflammatory models

Local inflammatory model is developed by the injection of chemical substance into the deep craniofacial tissues. For example, chemicals including CFA (complete Freund's adjuvant) [16,86,102,103], formalin [104–107], mustard oil [108,109], carrageenan [105,110,111], serotonin (5HT) [112,113], ATP [114,115], capsaicin [116,117], monosodium iodoacetate [80,118] and zymosan [105,119] have been used. In this article, we focus on two preclinical models produced by the local administration of CFA or formalin to discuss, because these models have been often employed to study the basis for TMD pain.

3.1.1.1. CFA model. Evidence indicates that CFA model shows increased nocifensive behaviors associated with deep craniofacial tissues with neural changes in the PNS and CNS, mimicking TMD myalgia, arthralgia and particularly osteoarthritis. In most experiments, CFA is injected into the TMJ or masseter muscle, and each experiment selects a certain time point after CFA injection, often employs later than 7 days.

Biochemical analysis reveals that CFA-evoked TMJ inflammation for 4 weeks increases inflammatory mediators such as IL-1 beta, IL-6, and TNF alpha in the rat TMJ [120]. These findings are similar with the features that TMD patients display inflammatory mediators to some extent in the deep craniofacial tissues [22,121], particularly in TMJ osteoarthritis [26,29].

Neural mechanisms in the PNS could be involved in the enhanced deep craniofacial nociception [14,100,101,122]. The elucidation of molecular basis for the deep craniofacial nociception is beyond the purpose of this article; however, recent findings indicate that peripheral TRPV1 [123], TRPA1 [114], TRPM2 [124], P2 × 3 [125,126], P2Y2 [127], and orexin [128] receptors play roles to mediate deep craniofacial nociception in CFA model.

CFA model shows neural changes in the CNS, resulting in increased deep craniofacial nociception, and evidence supports this notion. First, enhanced orofacial nocifensive behaviors are associated with changes in nociceptive neural activities in the trigeminal subnucleus caudalis (Vc) and upper cervical dorsal horn (C2) regions at 7–14 days after CFA injection, at which CFA-evoked local inflammation appears to be less [103,129,130]. The Vc and C2

regions are documented to play critical roles to regulate deep craniofacial nociception [90,101,102,122]. Recent reports reveal that increased neural activities in the Vc/C2 regions are mediated by NMDA receptor subunit, NR1 [131], serotonergic [130], cytokines [132], COX2 [133], and glial [134] mechanisms in the Vc and C2 region. Second, CFA model shows increased nocifensive behaviors outside the territory of trigeminal nerves including the hindpaw [135,136], while neural changes in the amygdala play critical roles on the induction of the widespread sensitization in CFA model [137]. Consequently, these characteristics of CFA model are consistent with the findings that TMD patients show hyperalgesia beyond the area of the deep craniofacial tissues [55].

CFA model also shows alterations in neuronal activities in the supra-spinal regions including the rostral ventromedial medulla (RVM) [6,138]. For example, the RVM has descending fibers that could modulate nociceptive responses in the Vc and C2 region. Similarly, imaging findings demonstrate that TMD patients display structural and functional changes in the brainstem associated with descending pain controls including the RVM [14,20,21,52]. Further, CFA-evoked TMJ inflammation for 10 days changes neural activities indicated by FosB/delta FosB expression in the amygdala and dorsal raphe nucleus [139]. These findings suggest that CFA model displays an altered neural function in the CNS associated with affective dimension of pain associated with deep craniofacial tissues.

The disadvantages of CFA model could be discussed. TMD patients do not show obvious inflammation even at the onset of pain, while CFA model displays a significant inflammation for 1–3 days, at least [103]. TMD patients complain a long-persistency of pain, whereas CFA-evoked increases in deep craniofacial nociception are returned to control levels within 4 weeks [103,140]. On the other hand, CFA model could mimic the arthritis type of TMD, since CFA-evoked TMJ inflammation displays time dependent changes in structures of the TMJ and nociception [120,131] and individuals presenting with RA often experience TMD pain [141].

Besides CFA model, additional models developed by local administration of proinflammatory mediators are discussed. Proinflammatory mediators including cytokines [142,143], growth factors [144,145], glutamate [83,101], acidic saline [114,122], and serotonin [146] are administered into the deep craniofacial tissues of animals, resulting in increased deep craniofacial nociception. The advantages for these experiments allow to investigate the neural mechanisms related to the specific receptor-mediated nociceptive processing in the deep craniofacial tissues. Further, this paradigm has been employed in clinical studies because of simple methodologies with increases in nociceptive responses in humans [23,35–41].

3.1.1.2. Orofacial formalin model. The other well-known local inflammatory model is the animals receiving formalin into the facial region [15,107,140]. The advantages of this model include that nociception in the deep craniofacial tissues could be quantified by the spontaneous behaviors in animals [107]. The temporal profiles of formalin-evoked behaviors are correlated with those of increases in neural activities in the Vc region [130]. Effects of local inflammation in the deep craniofacial tissues on formalin-evoked nociception are also determined using CFA model. Monoarthritis of the TMJ evoked by CFA shows a facilitation of the formalin-evoked nocifensive behaviors in the masseter muscle for more than 1 week, mediated by enhanced neural activities in the Vc region through the central 5HT3 mechanisms [129,130]. The disadvantages of formalin model are similar with those of CFA model, including a strong inflammatory reactions immediately after formalin injection.

3.1.2. Non-local inflammatory models

"Non-local inflammatory models" indicate that animals do not receive the pro-inflammatory agents, but are locally manipulated by minimum invasive treatments in the deep craniofacial tissues.

3.1.2.1. Jaw muscle pain (JM) and tendon of the masseter muscle ligation pain (TL) model. Two models for myogenic-related pain models for TMD are discussed here. First, repeated muscle contraction of masseter muscle by non-noxious electrical stimulation could cause hyperalgesia with no inflammation in the masseter muscle (Jaw muscle pain model: JM model) [147]. The validity for this model includes that excessive contraction of the masseter muscle induces tenderness in the masseter muscle [148] and increases jaw muscle activities seen in TMD pain [149]. Further, eccentric muscle contraction and rapids stretching of the masseter muscle induce hyperalgesia in the masseter muscle for 7 days [150]. Second, unilateral ligation of the tendon of the masseter muscle (tendon ligation model: TL model) could cause hyperalgesia in the masseter muscle for more than 8 weeks with enhanced neural excitabilities in the Vc region [151–153]. TL model produces long-term pain conditions, whereas, relatively, complicated and extensive surgical procedures are required compared with JM model [147].

3.1.2.2. Prolonged jaw opening model. TMD patients report a greater occurrence of events causing injury to deep craniofacial tissues including prolonged opening mouth and yawning [74]. A possible TMD pain model is developed by incorporations of such characteristic into the animals to determine the involvement of prolonged jaw openings in deep craniofacial nociception. For example, TMJ or masseter muscle-evoked neural activities indicated by c-Fos protein expression, are enhanced by repeated jaw openings in the rats [154,155]. Prolonged jaw opening model increases mechanical sensitivity in the face with elevated the level of inflammatory cytokines in the trigeminal root ganglion and upper cervical spinal cord [156], while repeated jaw openings also increase mechanical sensitivity in the facial region [157]. Interestingly, the neck inflammation increases mechanical sensitivities in the facial region evoked by prolonged jaw openings [158], suggesting that chronic tension in the neck and shoulder muscles could involve the nociception in the deep craniofacial tissues.

3.1.2.3. Occlusal interference model. In dental practice, occlusal interference is a common condition, and the proposed idea indicates that occlusal interference could induce jaw muscle activity, which might result in overworks of the muscles, pain and clicking of the deep craniofacial tissues [159,160]. Preclinical models evaluated the effects of occlusal interference on the facial nociception in the rats and showed that occlusal interference could increase in orofacial nocifensive behaviors [161]. Ample evidence, however, has indicated that occlusal interference could not to be causally related to TMD [18,162–164]. The validity for this model seems to be unclear to investigate the mechanism of TMD pain.

4. Preclinical models for psychological stress and deep craniofacial pain (Table 1)

There has been advanced in knowledge of the neural process underlying deep craniofacial nociception, psychological stress and their interaction [99]. Obviously, preclinical investigations contribute to understand the neural basis for psychological stress-induced increases in nociception [15,140,165]. Simple procedures to determine the basis for facilitatory effects of psychological stress on pain are to test if psychological stress models increase deep craniofacial nociception. The first business to conduct those experiments is to employ the stress models. Most stress models involve

the application of psychological and/or physical stressors repeatedly for several days to weeks in combination with a pain testing [140,165]. Currently, two stress models have been employed to test the interactions between psychological stress and deep craniofacial nociception.

4.1. Chronic restraint stress (CRS)

The chronic restraint stress (CRS) could be explained as a failure to adapt to stress conditions, causing adverse effects on brain function. In rodent models of CRS, physical restraints have been conducted by placing animals into restraint apparatuses for several hours each day for several weeks.

CRS consistently increases deep craniofacial nociception. For example, 40-day CRS results in increased orofacial nocifensive behaviors evoked by the TMJ injection of formalin [166,167]. Similarly, CRS for 7 days is sufficient to induce mechanical hyperalgesia in the masseter muscle [168,169], and CRS for 8 weeks enhances hyperalgesia in the masseter muscle evoked by occlusal interference [170].

The neural mechanisms for CRS-induced hyperalgesia in the deep craniofacial nociception have been demonstrated. CRS increases nocifensive behaviors in the masseter muscle, while CRS also induces structural, metabolic changes and oxidative damage in the masseter muscle [169,171,172]. CRS increases IL-I beta expressing satellite glial cells in the trigeminal root ganglion (TRG), the level of phosphorylated NR2B subunit and activation of astrocytic JNK in the Vc region, while blockade of IL-1 beta receptors in the TRG and that of NMDA receptors in the Vc region reduces masseter muscle nocifensive behaviors under CRS conditions [168,173,174]. CRS also affects neural function in the supra-spinal levels in the CNS. For example, CRS causes neural changes including serotonin (5HT) systems in the raphe magnus nucleus [175,176] of which descending pathways could regulate neural activities in the Vc region [14,100,122]. These reports support the notions that CRS-induced hyperalgesia is due to functional changes in the PNS and CNS associated with deep craniofacial nociception.

4.2. Repeated forced swim stress (FS)

Repeated forced swim stress (FS) model has been well documented as a rodent model of depression, and the immobility (non-swimming) behaviors have been quantified as behavioral despair on the assumption that the rodents have given up hope of escaping [177,178]. In this protocol, immobility time is quantified as depression-like behaviors. The typical posture of immobility is explained by floating in the water with only movements necessary to keep the face above the water surface [178].

FS is easy to use, has good reproducibility and is the most commonly employed in the drug screening tests of antidepressants, and the reduced immobility time could be reversed by the administration of antidepressants [177,178]. Currently, interpretation of immobility behaviors as depression-like behaviors is controversial [179,180]; however, FS is the useful model for studying the basis for stress-induced hyperalgesia, since FS (10–20 min/day) could consistently increase nociceptive responses in the animals. For example, FS for 2–3 days causes hyperalgesia in the hindpaw, increased neural activities in the lumbar dorsal horn [181,182] and in the supra-spinal areas [183,184].

Facilitatory effects of FS on deep craniofacial nociception have been investigated. FS enhances neural activities evoked by TMJ stimulation in the Vc region [185–187] and affects molecular mechanisms in the Vc region indicated by increases in the level of phosphorylated-cyclic adenosine monophosphate response element-binding protein (CREB), neurokinin 1 receptor mRNA [188] and cytokines [189].

Antidepressant agents inhibit enhanced masseter muscle-evoked nociceptive neural activities in the Vc region after FS [185]. Blockade of 5HT3 receptors in the Vc region inhibits enhanced TMJ-evoked neural activities in the rats after FS [190]. FS also increases neural activities in the nucleus raphe magnus evoked by masseter muscle stimulation with increases in the number of 5HT expressing neurons [191]. These findings indicate that FS causes dysfunction of descending pain controls associated with deep craniofacial nociception.

Further, comorbidities of the jaw muscle pain and other pathological conditions have been demonstrated under FS conditions [192,193]. For example, although masseter muscle inflammation alone does not cause visceral hypersensitivity, exposure to FS causes visceral hypersensitivity in the masseter muscle pain model [193]. FS for 10 days increases mechanical and thermal sensitivity of the hindpaw after CFA-evoked TMJ inflammation with down-regulation of several 5HT receptor subtypes [194].

Collectively, CRS and FS models show increases in deep craniofacial nociception through neural changes in the PNS and CNS, while these findings are consistent with the characteristics of painful TMD conditions. Limitations could be raised regarding the clinical relevance. In a social life, exposures to such stressors like restraint of the human body for weeks and forced swimming conditionings for days could rarely occur.

4.3. Social defeat stress (SDS)

Social conflicts often happen in a human society, which could be unavoidable stress, leading to reduce the quality of life [195]. Repeated social defeat stress (SDS) conditionings resulting from the exposure of the rodent to multiple aggressive social encounters appear to be relevant stressor mimicking common types of psychosocial stress seen in humans [196,197]. These findings indicate that SDS models could be more relevant for the psychological stress conditions in human life compared with CRS and FS models. Further, SDS increases nociceptive responses in inflammatory- [198,199], lumbar disk herniation- [200], postsurgical- [201], visceral- [202] pain and migraine models [203]. Recently we demonstrate that SDS conditionings for 10 days are sufficient to increase the masseter muscle nociception [204], indicating increases in the deep craniofacial nociception under psychosocial stress conditions. However, the underlying mechanisms for this remain unclear.

5. How to identify the pain in the deep craniofacial tissues in the preclinical models? (Table 2)

In preclinical models, pain needs to be identified by the objective responses such as “evoked pain response” (see Section 5.1) and “non-evoked pain response” (see Section 5.2), since animals do not express their pain verbally. “Evoked-pain response” is identified by nocifensive responses evoked by external stimulations. On the other hand, outcomes of “non-evoked pain” response attempt to measure voluntary or intentionally behaviors.

5.1. Evoked pain-like responses

Preclinical pain models in the deep craniofacial tissues often employ the acute assay with the induction of a brief pain-like responses in the TMJ and jaw muscles. The nociceptive responses evoked by mechanical and heat (cold) stimulation have been widely used to quantify nociceptive responses; however, limitations should be considered. First, the duration of stimulus-evoked pain-like response is relatively short. Second, in the spinal pain model, withdrawal nocifensive behaviors in the hindpaw are mediated through the reflex circuits within the spinal cord and brainstem

Table 2
The procedures to identify deep craniofacial nociception discussed in this article.

Response types	Measures
Reflex	• Withdrawal/shaking • Grooming/rubbing
Spontaneous	• Bite force • Meal pattern • Grimace scale
Others	• Operant pain assay • Conditioned place avoidance

rather than the higher brain centers [96], indicating that the activated areas in the CNS might be smaller than those under chronic pain conditions. Third, mechanical stimulation to the deep craniofacial tissues has been often employed to induce pain in the TMJ and jaw muscle. These procedures, however, could activate both non-noxious and noxious sensory receptors in the skin. Most preclinical models above, show increases in allodynia-like responses in the facial skin; however, evidence reports that TMD patients display reduced tactile sensory responses and changes in cortical responses to tactile stimulation in the facial skin [57,205]. Fourth, the common characters of TMD are spontaneous pain or pain with jaw opening and mastication, whereas stimulation-evoked pain-like responses do not assess pain itself, but hypersensitivity, accompanying increased nociception.

5.2. Non-evoked pain-like responses

"Non-evoked pain" protocols have been conducted to quantify the deep craniofacial nociception, such as the measuring the changes in orofacial function as well as those in affective responses associated with pain. These procedures are recognized to be clinically relevant way by not relying on external stimulation-evoked measurements of nociception.

5.2.1. Bite force and meal pattern analysis

Specific functions of the orofacial areas such as bite force could determine the nociception in the deep craniofacial tissues of the animals [151,206]. The validity for usage of bite force in the animals could be explained by the evidence of a reduction of bite force in painful TMD patients [207,208]. Biting behaviors are measured by changes in the bite force in awake animals, which are trained to bite a force transducer. Preclinical models display decreases in voluntary biting behaviors [151,209]. Another procedure using orofacial performance as an objective measure of masticatory function is to assess the effects of meal pattern behaviors indicated by meal duration, total number of meals and total time spent eating [80]. Preclinical studies demonstrate that TMD pain models decrease the amount of food intake and increased meal duration [80,210]. Both bite force and meal pattern analyses could identify nociception specific to the deep craniofacial tissues, but limitations cannot be ignored including the requirements of training animals and specific devices. Experimental procedures in details are described elsewhere [80,151]

5.2.2. Grimace scale

The grimace scales could identify characteristics of the facial expression associated with nociception, which have been considered to represent a measure of the affective responses to pain in the rodents [211]. The grimace scales adapt that scoring to utilize facial features as indicators to assess pain, and are correlated with deep craniofacial pain in the rodents [151]. Obviously, these procedures have advantages to identify spontaneous pain, particularly; however, limitations could be documented. First, the elevated grimace scale scores are observed for up to 7 days, indicating that long-term monitoring of spontaneous pain seems to be still challenging. Second, the time and effort are required to manually score the results [212]. Further, no study has examined the grimace scale associated with deep craniofacial nociception under psychological stress conditions.

5.2.3. Operant measures of pain assay

Operant measures of pain assay (and the conditioned place aversion strategy shown below [213]) have significant abilities that can evaluate the affective aspects of pain compared with the paradigms of evoked-pain responses [97,214–216]. This system employs a reward-conflict paradigm in which animals select between obtaining a reward in the presence of nociceptive stimulation and avoiding both stimulus and the reward. In the preclinical model for TMD pain [209,210], to have the reward, the animals need to poke its face through an opening equipped with a heat stimulation device so that the aversive stimulation is obtained at the same time as the reward. The advantages for this procedure include that animals can control over the amount of nociceptive stimulation, indicating that animals could modify their behaviors based on the higher level of the brain processing [217]. Because the affected areas in the CNS mediating chronic pain could be larger compared with those acute pain, the operant pain assay could assess CNS mechanisms more comprehensively.

5.2.4. Conditioned place aversion strategy (CPA)

Several studies use conditioned place aversion strategy (CPA) to determine the basis for TMD pain using preclinical model [151,209]. Animals have a choice to avoid painful stimuli when they stayed in preferred area, which might assess the affective components of pain mediated by supra-spinal integration [96,213] The behavioral procedures in details have been described elsewhere in the model for TMD pain such as TL model (see Section 3.1.2) [151,209]. In brief, according to Guo et al. [151], the light and dark rooms are connected, animals could freely move to either room. Then, noxious stimulation is applied to the face above the tendon injured area, when animals stay in the dark room. Rodents normally prefer to stay in the dark area, and staying in the preferred dark room is associated with an aversive and painful stimulus after tendon injury, and the injured animals are forced to decide whether to remain in the dark room or leave for the light room to avoid the aversive stimulation to the face. Quantification of the changes in time spent in the light room is considered as an indication of the pain aversive conditions, while the TL pain model shows increases in the time spent within the light area compared with naïve animals [151]. CPA paradigm appeares to be convenient to identify the affective component of deep craniofacial nociception [213].

6. Conclusion

Each preclinical model shows similarities with the pathophysiology of painful TMD indicated by neural changes in the PNS and CNS, resulting in increases in nociception [14,15,122,140]. However, the gaps are still existing. Here, several notions that further animal models need to possess are raised. First, preclinical models need to show increased nocifensive behaviors in the deep craniofacial tissues associated with neural changes, particularly in the CNS with less or without local inflammation except the case of the osteoarthritic TMD. Second, risk factors should be incorporated into an animal, since the etiology for TMD pain is multi-dimensional. Third, preclinical models need to have similar biochemical and neuro-functional characteristics in the PNS and CNS with painful TMD patients. Accordingly, imaging approaches have significant

potentials to resolve these gaps, since results could be comparable between them. Fourth, "evoked-pain" like responses are necessary to understand the sensory-aspect of pain, while several measurements of "non-evoked pain" responses could be assessed to determine the unpleasant aspect of pain. Further, nociceptive responses in a manner consistent with the orofacial function specific to TMD pain including the bite force and meal pattern analyses could be helpful, if available. Finally, the way of pain induction in the deep craniofacial tissues needs to reflect pathophysiological features in TMD pain conditions, which could facilitate predictability of clinical outcomes. Researchers need to continue developing the ideal preclinical models with the critical assessments to facilitate better understandings of TMD pain.

Conflict of interest

We declare no conflicts of interest associated with this manuscript.

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