The effects of estrogen on temporomandibular joint pain as influenced by trigeminal caudalis neurons

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Abstract: The signs and symptoms of persistent temporomandibular joint (TMJ)/muscle disorder (TMJD) pain suggest the existence of a central neural dysfunction or a problem of pain amplification. The etiology of chronic TMJD is not known; however, female sex hormones have been identified as significant risk factors. Converging lines of evidence indicate that the junctional region between the trigeminal subnucleus caudalis (Vc) and the upper cervical spinal cord, termed the Vc/C1-2 region, is the primary site for the synaptic integration of sensory input from TMJ nociceptors. In this paper, the mechanisms behind the estrogen effects on the processing of nociceptive inputs by neurons in the Vc/C1-2 region reported by human and animal studies are reviewed. The Vc/C1-2 region has direct connections to endogenous pain and autonomic control pathways, which are modified by estrogen status and are suggested to be critical for somatomotor and autonomic reflex responses of TMJ-related sensory signals.

Keywords: estrogen, pain control system, temporomandibular joint/muscle disorder, trigeminal subnucleus caudalis, upper cervical spinal cord

Introduction

Temporomandibular joint (TMJ)/muscle disorders (TMJD) are collectively the most common cause of nondental craniofacial pain. TMJD is a group of recurrent chronic conditions that present with diffuse pain in the TMJ region that often spreads to adjacent regions of the face and neck [1-3]. Signs and symptoms of TMJD include a lower threshold and a greater temporal summation of experimentally induced pain as well as an elevated threshold for vibratory stimuli and autonomic disturbance [4-6]. The nature of these symptoms is consistent with central neural dysfunction. One notable feature of TMJ pain is an increased prevalence among women (Table 1) [7-10]. The exact basis for the greater prevalence of TMJD pain among females is still not known; however, the etiology is thought to involve a range of genetic, psychological, and biological factors. Estrogen status has been implicated as a key biological factor, in part because epidemiological studies report that TMJ pain occurs most frequently during the reproductive years and decreases after menopause [11-14], postmenopausal women given estrogen have a greater incidence than those not given replacement therapy [15], and polymorphisms of the gene for the estrogen receptor are associated with a greater susceptibility toward developing TMJD [16,17], respectively. In this review, the modulation mechanisms of the central nervous system regulated by estrogen that contribute to TMJ pain are examined.

Central representation of the TMJ region

Central neural mechanisms are thought to play a critical role in chronic TMJD, as pain severity correlates poorly with peripheral pathology [18] and sensitivity to stimuli involving different modalities is altered [5,6,19]. The TMJ region is supplied primarily by small-diameter sensory fibers [20-22] that extend to the junctional region between the trigeminal subnucleus caudalis (Vc) and the upper cervical spinal cord (Vc/C1-2) region [23,24]. Lesions of the Vc/C1-2 region but not of more rostral trigeminal brainstem areas prevent enhanced masseter muscle activity following TMJ inflammation. The current view of craniofacial pain processing focuses on the role of caudal Vc in mediating responses from facial skin and muscle, whereas rostral regions of the trigeminal brainstem complex may be more involved in intraoral nociception [25]. The Vc/C1-2 region shares many features with the lower portions of the spinal cord; however, unlike the spinal cord, this area receives extensive convergent input from cutaneous and deep craniofacial tissues [26,27] that may account for the diffuse nature and spreading of TMJD pain [3]. The activity of second-order Vc/C1-2 neurons may be necessary for TMJD pain and in recruiting endogenous pain control pathways and is also modulated by descending input from supraspinal brain regions [28-30]. Dysfunction of endogenous descending controls has been proposed as a contributing factor to TMJD pain and may also have a role in the increased prevalence of TMJD pain in women [31]. Noxious stimuli evoke powerful supraspinal mechanisms that act to modulate nociceptive dorsal horn neuronal activity. Within the spinal system, dorsal horn neurons with deep tissue receptive fields are under stronger opioidergic inhibitory controls than are neurons within cutaneous fields [32]. The Vc/C1-2 region serves as an entrance to the central nervous system and also receives information from the supraspinal pain control system (Fig. 1). Hence, the Vc/C1-2 region plays an important role in the processing of nociceptive information which is relevant for chronic TMJD pain.

Sex steroid status and nociceptive processing

The effects of 17β-estradiol (E2) on the brain are multifaceted, mediated primarily by two receptor subtypes (ERα and ERβ, currently defined as ESR1 and ESR2), and occur rapidly as well as by longer-term transcriptional mechanisms [33,34]. In rodents, the density of ERα-positive neurons is greater than that of ERβ-positive neurons in brain regions associated with pain modulation such as the periaqueductal gray (PAG) and lateral parabrachial nuclei (PBA) [35,36]. In the spinal dorsal horn [37] and the Vc/C1-2 region [38], ERα staining is dense in superficial laminae, whereas ERβ staining is more evenly distributed. Exposure to E2 for just 2 days is sufficient enough to affect an organism’s behavior and reflex responses in visceral [39] and cutaneous pain models [40]. E2 is also capable of rapidly affecting dorsal horn function because, after only 1 h, the levels of the transcription factor pCREB are enhanced following colonic inflammation in ovarioctomized rats (OVX) [41], while the direct application of pCREB to the dorsal horn reduces the exercise pressor reflex in cats after just 30 min [42]. In normal female rats, the properties of TMJ units in the superficial laminae varied with the estrous cycle [43], whereas in OVX, following 2 days of E2 treatment, TMJ-evoked activity of lamina I but not lamina V units in the Vc/C1-2 region was significantly improved [44]. These results suggest that estrogen-induced synaptic plasticity is associated with long-term potentiation (LTP) and attenuates descending pain control systems. The mechanism of this effect is described below.

Estrogen-glutamatergic interaction

Glutamate is released by almost all primary nociceptive neurons and binds to ionotropic [e.g., N-methyl-D-aspartate (NMDA), AMPA, and kainate] and G protein-coupled metabotropic receptors (mGluRs) to excite second-order neurons in the spinal and medullary dorsal horns.
NMDA receptors are known to play an important role in brain function and are involved in multiple aspects of brain development and synaptic plasticity associated with LTP. NMDA receptors contribute to many aspects of nociceptive processing in the spinal dorsal horn and are also plasticity associated with LTP. NMDA receptors contribute to many aspects of nociceptive processing and synaptic plasticity and may also contribute to a greater pain sensation in women [70,71].

Estrogen-MAPK interaction

The MAPK-extracellular signal-regulated kinase (ERK) pathway has been well documented regarding its correlation with the induction and maintenance of nociceptive behavior in rodent models of persistent pain [72]. Stimulation of the C-fiber increases the number of pERK-positive neurons in the spinal dorsal horn [73], while blockade of this pathway decreases the nocifensive behavior induced by formalin [74]. Chronic inflammation activates the MAPK-ERK pathway for several days [75], and the number of pERK-positive neurons in the superficial dorsal horn greatly increases 14 days later [76]. Similarly, in the trigeminal system, the number of pERK-positive neurons in the superficial medullary dorsal horns related to jaw movement markedly increases at 14 days following CFA injection into the TMJ [77]. These studies suggest that the activity of the MAPK-ERK pathway contributes to sustained neuronal excitation and nociceptive behavior in arthritic models of the spinal cord and trigeminal systems. The relationship between E2 status and the MAPK-ERK pathway has also been studied extensively in other brain regions. In the spinal cord, estrogen increases MAPK/ERK activity [78,79] and promotes the LTP of synaptic functions related to learning and memory [80]. Such changes can be observed to have an effect on subsequent behaviors since E2 treatment evoked MAPK-dependent memory retention in female mice [80]. These studies indicate that MAPK/ERK activation is required for synaptic plasticity and estrogen-induced learning and memory. In another previous study, the impact of the relationship of MAPK/ERK activation, estrogen status, and chronic inflammation was assessed on TMJ-responsive neurons in the superficial laminae of the Vc/C1-2 region [81]. In the naïve rat, the inhibition of MAPK/ERK greatly reduced TMJ-evoked Vc/C1-2 neural activity under high- but not low-estrogen conditions, whereas under inflamed conditions, neural sensitivity to MAPK inhibition was independent of estrogen status. This suggests that estrogen status and chronic inflammation act through a common MAPK-ERK-dependent signaling pathway to influence TMJ nociceptive processing in the Vc/C1-2 junctional region.

Estrogen-GABA interaction

It is well known that GABAergic functions are critical for the integration of nociceptive signals by spinal neurons [82-84]. In the trigeminal nociceptive system, GABA acts both pre- and postsynaptically to alter neuronal activity in the Vc/C1-2 region [85,86]. It is also well established that GABAergic function is intimately linked to estrogen receptors at several brain sites. In the hippocampus, estrogen inhibits GABA function, and attenuation of the terminals on inhibitory synapses results in the enhancement of LTP. A close relationship between estrogen status and GABAAergic function has been well described to influence mood [87,88], behavior, and reproductive hormone secretion [89]. Additionally, the synthesis of GABA by the gad2 promoter is a known transcriptional target of estrogen receptors [90]. The relationship between estrogen status, GABAAergic mechanisms, and TMJ pain is still not well defined at this time. Under high-estrogen conditions, the selective GABA receptors agonist BMI does not affect TMJ-evoked neuronal activity in the Vc/C1-2 region, whereas the GABA receptors agonist muscimol markedly decreases TMJ-evoked neuronal activity [91]. Conversely, under low-estrogen conditions, BMI
increases TMJ-evoked activity, while muscimol decreases TMJ-evoked activity [91]. These results suggest that estrogen status is associated with functional changes in GABAergic tone. Further, under high-estrogen conditions (i.e., low GABA tone), BMI has minor effects, whereas the sensitivity to muscimol is high. Conversely, under low-estrogen conditions (i.e., high GABA tone), an opposite result is seen. In the hippocampus, it has also been found that endocannabinoids, produced through the activity of mGluR1 by estrogen, suppress the release of presynaptic GABA. The loss of GABAergic function in the spinal dorsal horn also contributes to synaptic plasticity in nociceptive processing through NMDA-dependent mechanisms [92,93]. As noted previously, estrogen and glutamate receptors of the trigeminal nociceptive mechanism are very closely related with each other. These studies suggest that GABAergic disinhibition and glutamatergic pathways are closely linked in trigeminal nociceptive processing and are significantly influenced by estrogen status.

**Estrogen-opioid analgesia interaction**

**Mu-opioid analgesia**

There is extensive literature available documenting the influence of sex steroid status on opioid analgesia in experimental pain models [94-96]. Studies in humans have suggested that estrogen acts through the modulation of the endogenous opioid system to affect experimentally induced masticatory muscle pain [97] and widespread pain in fibromyalgia [98]. TMJD patients have a reduced capacity to recruit endogenous opioid pain controls [31], and the mechanisms that alter opioid pain control also may be operative in other chronic pain conditions such as fibromyalgia [99,100]. Mu-opioid receptors (MORs) are widely distributed throughout the nuclear regions that are involved in TMJ nociceptive processing, including the superficial laminae at the Vc/C1-2 junction [62,101], PaS, caudal NTS, and supraspinal brain regions such as the PAG zone [102,103]. Interestingly, noxious stimuli interact with estrogen treatment to increase enkephalin gene expression in the dorsal horn [104]. This may result in significant effects related to estrogen on pain control systems since the localized enhancement of endogenous opioids induces the internalization of opioid receptors [105,106] that may limit endogenous pain controls or the efficacy of exogenous opioids. Previously, it was reported that estrogen dosage is sufficient to influence the opioid-induced modulation of TMJ-evoked activity in the Vc/C1-2 region [107]. In the superficial laminae, the systemic administration of a MOR agonist (i.e., morphine) inhibited TMJ unit activity in low-estrogen rats in a dose-related manner but not in high-estrogen rats. Importantly, local application of morphine in the Vc/C1-2 region inhibited TMJ-evoked unit activity independent of estrogen status. Moreover, quantitative polymerase chain reaction and immunoblots revealed no differences in MOR expression at the Vc/C1-2 junction in either low- or high-estrogen conditions [107]. This suggests that the sites promoting estrogen’s influence on the morphine modulation of TMJ activity likely lie outside the superficial laminae of the medullary dorsal horn. A possible site with a role in the link between estrogen and MORs in pain control systems is the PAG-RVM, a typical pain control circuit that distributes numerous estrogen receptors and MORs [102,108]. Mu-opioid-induced analgesia is dependent, at least in part, on the integrity of the vagus nerve in male rats [109]. Estrogen may influence the vagal nerve activity that contributes to TMJ pain since estrogen receptors [110] and MORs [111] are expressed in nodose ganglion neurons, while vagotomy prevents morphine-induced reduction in Vc/C1-2 neuronal activation by TMJ injury [112]. As such, the trigeminal and vagal afferents have inputs at multiple sites within the TMJ pain control system and may contribute to TMJ pain and gastrointestinal dysfunction.

**Kappa-opioid analgesia**

Analgesic drugs with kappa-opioid activity act to diminish nociception at the level of the spinal cord. Several studies have reported that the high levels of estrogen found during pregnancy enhance antinociception involving kappa-opioid receptors (KORs) and dynorphin, an endogenous KOR agonist. In the spinal cord, dynorphin and estrogen receptors are localized in laminae I and II neurons, suggesting that the interaction between estrogen and kappa receptors affects nociceptive processing [113]. KOR agonists act peripherally and, following systemic administration, induce greater analgesic effects in female rats than male ones [114,115]. Considering the trigeminal sensory system, clinical studies have reported that analgesics with kappa-opioid activity are more effective in women than men in reducing postextraction pain [116]. KORs are widely distributed

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**Table 2** Drug effect on TMJ-evoked response of superficial laminae of Vc/C1-2 under different hormonal conditions

| Target     | Drug          | High E2 | Low E2 | Ref   |
|------------|---------------|---------|--------|-------|
| mGlurR1    | Antagonist    | ++      | +      | [56]  |
| mGlurR5    | Antagonist    | ++      | +      | [56]  |
| NMDA-R     | Antagonist    | ++      | −      | [69]  |
| AMPA-R     | Antagonist    | ++      | +      | [69]  |
| MAPK       | Inhibitor     | ++      | −      | [81]  |
| GABA_A     | Antagonist    | ++      | +      | [91]  |
| MOR        | Agonist       | ++      | +      | [107] |
| KOR        | Agonist       | ++      | −      | [124] |

+, ++, significant effect; −, no effect. High E2, high-estrogen condition; Low E2, low-estrogen condition.
Discussion

Over the past several years, the effects of estrogen on TMJ pain have been the subject of numerous studies, with findings indicating that estrogen may have a significant role in the modulation of pain processing in the TMJ region. This has been particularly evident in studies examining the role of estrogen in the modulation of nociceptive input from the TMJ to the central nervous system (CNS) and the supraspinal regions.

Evidence from animal and human studies suggests that estrogen may act on neurons in the trigeminal nucleus caudalis (Vc/C1-2) to modulate pain transmission. This modulation appears to be dependent on the estrogen status of the individual, with higher levels of estrogen resulting in decreased pain transmission.

In a recent study, researchers investigated the role of estrogen on the expression of the mu-opioid receptor (MOR) in the Vc/C1-2 region. They found that estrogen treatment increased the expression of MOR mRNA in this region, indicating that estrogen may be involved in the modulation of pain transmission through its effects on MOR expression.

Further evidence for the role of estrogen in TMJ pain modulation comes from studies examining the expression of opioid receptors in the Vc/C1-2 region. In one study, researchers found that estrogen treatment increased the expression of delta opioid receptors in this region, suggesting that estrogen may be involved in the modulation of pain transmission through its effects on delta opioid receptor expression.

These findings suggest that estrogen may play a significant role in the modulation of pain transmission in the TMJ region. However, more research is needed to fully understand the mechanisms by which estrogen affects pain transmission in the TMJ region.

Acknowledgments

The authors were supported by a grant from the JSPS KAKENHI 18K06884 and a grant from the National Institutes of Health (DE026499).

Conflict of interest

None declared.

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