## ULF-TENS on Myogenous Temporomandibular Dysfunction

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Ultra-low frequency transcutaneous electrical nerve stimulation (ULF-TENS) is an active therapeutic device that affects relaxation of masticatory and mandibular postural muscles through applying low-frequency, low current stimulation of the mandibular division of the trigeminal nerve and a branch of the superficial facial nerve.

masticatory myofascial pain	parabrachial nucleus	rostral ventromedial medulla
temporomandibular disorder	ultra-low frequency trans	scutaneous electrical nerve stimulation

## 1. Introduction

According to available literature<sup>[1][2][3][4]</sup>, Ultra-low frequency transcutaneous electrical nerve stimulation (ULF-TENS) seems to be a valid support in the management of TMD patients with more 'relaxed' muscles <sup>[5][6][7][8]</sup>, but some patients get worse after ULF-TENS, presenting an increase in electromyographic activity<sup>[9][10]</sup>. Currently, the mechanisms responsible for the analgesia produced by ULF-TENS remain unclear, especially regarding the involvement of connections in central pain-modulating neurons.

Orofacial pain resulted from TMD may involve the parabrachial nucleus that forms ascending trigeminoparabrachial nociceptive pathways to convey the MMP-induced nociception to higher brain circuits for developing the affective dimension of pain, emotional, and autonomic disturbances<sup>[11][12][13]</sup>. However, there is growing evidence that the parabrachial nucleus is one of the main connections with the descending pain-modulating systems, best characterized by abundant projections of parabrachial nucleus to the rostral ventromedial medulla involved in pain modulation <sup>[14]</sup>. An alteration in the descending inhibitory or excitatory influences from some structures such as the rostral ventromedial medulla and central opioid pathway seems to be the most powerful in reducing pain behavior and nociceptive neuronal activity<sup>[15]</sup>. Therefore, modulation of both parabrachial nucleus and rostral ventromedial medulla that are involved in pain-modulatory circuits can be possible mechanisms behind therapy for MMP.

Substance P (SP) is one such biochemical richly distributed in the parabrachial nucleus and thought to be released from primary afferent terminals by noxious or painful stimuli. Its neuromodulation on transmission in the parabrachial nucleus has been reported <sup>[16][17]</sup>. Activation of  $\mu$ -opiate receptors (MOR) in interneurons produces hyperpolarization of neurons, leading to inhibition of firing and modulation of responses to SP, thereby blocking pain transmission. Increased expression of SP in the parabrachial nucleus after tetanic contraction-induced MMP in rat model has been previously identified. In view of these results, this study hypothesizes that ULF-TENS at myofascial trigger points activates neurons in the rostral ventromedial medulla affecting its expression of c-Fos,

enhances MOR expression in the parabrachial nucleus, as well as reduces SP expression in the parabrachial nucleus, thus alleviating MMP. Therefore, the aim of this study is to examine the effects of ULF-TENS on electrophysiological activities and functional movements of masticatory muscles, as well as the biochemical alterations in both parabrachial nucleus and rostral ventromedial medulla in animal models of MMP.

### 2. Effects of ULF-TENS on Electrophysiology of Masseter Muscle after MMP Induction

Figure 1A–D show serial changes of EPN activities from myofascial trigger points of masseter muscle recorded at the focal hypoechoic area (Figure 1E) under ultrasonic guidance before, after MMP/sham-MMP induction, and after ULF-TENS/sham ULF-TENS treatment in the four groups. Before MMP induction, there was no significant difference in EPN prevalence among the groups ( $\chi 2(3) = 7.32$ , p = 0.06, Table 1). Significant differences among the four groups were found after MMP induction at both time points of pre-treatment ( $\chi 2(3) = 29.37$ , p = 0.000002) and post-treatment ( $\chi 2(3) = 25.87$ , p = 0.00001). After MMP induction, EPN prevalence in both MU and MsU groups were significantly increased compared with that in sMU and sMsU group, indicating marked increase in mean EPN prevalence in masseter muscle after chronic maximum tetanic eccentric contraction (all p < 0.0083, Figure 1F, Table 1). After treatment, the MMP-induced increment of EPN prevalence was reduced in the MU group, indicating no statistically significant difference compared with that in sMU and sMsU groups (both p > 0.0083, Figure 1F). However, EPN prevalence was still significantly higher in the MsU group than in the other groups (all p < 0.0083, Figure 1F). There were significant differences between the MU and MsU groups (Z = -3.82, p = 0.00013). Significant difference was found in the difference of improvement from pre-treatment to post-treatment time points between MU and MsU groups (Z = -3.82, p = 0.00014, Cohen's d. = -4.097).

There were significant differences in EPN prevalence among those recorded before induction, before treatment, and after treatment conditions in both MU ( $\chi$ 2(2) = 15.79, p < 0.017) and MsU ( $\chi$ 2(2) = 15.73, p < 0.017) groups (Table 1).

		Pre- Induction	Pre- Treatment	Post- Treatment	<sup>2</sup> Differences among Timepoints, <i>p</i> Value
EPN prevalence	MU	27.30 ± 5.68	52.60 ± 4.77 *†§	28.10 ± 6.03 ‡	0.00037
(%)	MsU	29.40 ± 7.07	51.20 ± 8.94 * <sup>†§</sup>	54.50 ± 6.17 * <sup>†§  </sup>	0.00038
	sMU	22.70 ± 4.64	25.30 ± 6.00	24.80 ± 4.52	0.04214 (NS)
	sMsU	28.10 ± 4.01	27.4 ± 4.76	28.20 ± 2.53	0.86687 (NS)

 Table 1. The prevalence of endplate noise and maximum jaw-opening distances at each evaluation time in four groups.

		Pre- Induction	Pre- Treatment	Post- Treatment	<sup>2</sup> Differences among Timepoints, <i>p</i> Value
<sup>1</sup> Differences amon <i>p</i> value	g groups,	0.0623 (NS)	$1.87 \times 10^{-6}$	1.02 × 10 <sup>-5</sup>	
Jaw-opening distance	MU	2.23 ± 0.16	1.92 ± 0.16 * <sup>†§</sup>	2.15 ± 0.08 <sup>‡</sup>	0.00183
(cm)	MsU	2.21 ± 0.15	1.95 ± 0.12 * <sup>†§</sup>	1.93 ± 0.09 * <sup>†§  </sup>	0.00037
	sMU	2.16 ± 0.19	2.20 ± 0.19	2.24 ± 0.18	0.13904 (NS)
	sMsU	2.22 ± 0.12	2.20 ± 0.11	2.26 ± 0.15	0.04436 (NS)
<sup>1</sup> Differences amon <i>p</i> value	g groups,	0.88 (NS)	$3.03 \times 10^{-5}$	$1.61 \times 10^{-4}$	

# **3. Effects of ULF-TENS on Maximal Jaw-Opening Distance after MMP Induction**

There were significant differences in the maximum jaw-opening distances among those recorded before induction, before treatment, and after treatment conditions in both of MU ( $\chi^2(2) = 12.60$ , p < 0.017) and MsU ( $\chi^2(2) = 15.79$ , p < 0.017) groups (**Table 1**). The maximum jaw-opening distances were significantly decreased in both MU and MsU groups after MMP induction compared with those before induction (both p = 0.005, **Table 1**). However, there were no significant changes after induction in both sMU and sMsU groups when compared with values before induction (p > 0.017, **Table 1**). After treatment, maximum jaw-opening distances were increased in the MU group when compared with those after induction (Z = -2.70, p = 0.00687); however, the distances were still significantly more limited in the MsU group than in the other groups (all p < 0.0083, **Figure 2**). Significant difference was found in the difference of improvement from pre-treatment to post-treatment time points between MU and MsU groups (Z = -3.33, p = 0.00086, Cohen's d. = 1.7995).



**Figure 2.** Maximum interincisal distance measured using Vernier caliper in four groups. Data of maximum jawopening distance are presented as mean  $\pm$  SD at the pre-induction, pre-treatment, and post-treatment time points; \*: *p* < 0.0083 indicates significant differences between either sMU or sMsU group tested by Mann–Whitney test.

### 4. Expressions of SP-like and MOR-like Immunoreactivity in Parabrachial Nuclei

**Figure 3** shows immunohistochemical expressions of SP proteins in the parabrachial nucleus of each group. Neurons stained with SP-LI were visualized in high-density brown precipitates, along with strong positive pixels of nuclear and cytoplasmic stainings, especially in the lateral parabrachial nucleus. There was higher expression in ventral and internal parts of the lateral parabrachial nucleus in MU rats (**Figure 3**A). By contrast, the most prominent SP-LI expressed throughout the lateral parabrachial nucleus including ventral, internal, central, superior, and external parts at very high density in MsU rats (**Figure 3**B). Only sparse expression of SP-LI was found in ventral parts of lateral parabrachial nucleus in sMU and sMsU rats (**Figure 3**C,D, respectively). Qualitative analysis of SP-LI in the parabrachial nucleus showed different immunoreactivity patterns among the four groups (**Figure 3**E). Quantitative analysis revealed significantly greater increase of SP-LI in the parabrachial nucleus in the MU and MsU groups than in the sMU and sMsU groups (both *p* < 0.0083, **Figure 3**F, **Table 2**). There was significant difference in SP expression between MU and MsU groups (Z = -3.79, *p* = 0.000148, Cohen's d. = -3.42).



**Figure 3.** Representative SP-LI staining in sections of parabrachial nucleus (PBN) in rats of MU (**A**), MsU (**B**), sMU (**C**), and sMsU (**D**) groups. The distributions of SP-LI staining area are mostly located in lateral and medial parabrachial nucleus (LPBN and MPBN) in MU, sMU (solid dots), and sMU (open dots) groups (**E**). Data of SP-LI in parabrachial nucleus is presented mean  $\pm$  SD and values with different superscripts (e.g., a vs. b and b vs. c) indicate significant differences (p < 0.0083) for all possible pairwise comparisons of means tested by Mann–Whitney tests (**F**). Scale bars, 250 µm.

**Table 2.** The substance P (SP), μ-opiate receptors (MOR), and c-Fos immunoreactivity in the parabrachial nucleus and rostral ventromedial medulla in four groups.

	MU	MsU	sMU	sMsU	<sup>1</sup> Differences among Groups, <i>p</i> Value
Parabrachial nucleus (%)					
SP	21.18 ± 2.19 * <sup>†‡</sup>	49.33 ± 11.42 <sup>†‡</sup>	9.89 ± 0.35	8.49 ± 2.63	<i>p</i> < 0.0001



**Figure 4.** Representative MOR-LI staining in sections of lateral parabrachial nucleus (LPBN) in rats of MU (**A**), MsU (**B**), sMU (**C**), and sMsU (**D**) groups. The distributions of MOR-LI staining area are mostly located in LPBN in MU and sMU groups (triangles, **E**). Data of MOR-LI in LPBN are presented mean  $\pm$  SD and values with different superscripts (e.g., a vs. b and b vs. c) indicate significant differences (p < 0.0083) for all possible pairwise comparisons of means tested by Mann–Whitney tests (**F**). Scale bars, 250 µm.

## 5. Conclusions

MMP is a multifactorial disorder, mostly involving occlusal, skeletal, and psychological disturbances manifested in muscular structures. This research found increased MOR-LI and reduced SP-LI in the parabrachial nucleus and increased c-Fos-LI in the rostral ventromedial medulla, as well as improvements of jaw-opening distance and EPN prevalence after ULF-TENS treatment in the MMP animal model, indicating that MMP can be modulated by ULF-TENS. It is the first study demonstrating the underlying mechanism of ULF-TENS, which is probably beneficial to management of MMP. More biochemical studies may further reveal a central nociceptive transmission mechanism that can provide more information of such neuroplasticity alterations arising from effects of ULF-TENS on myofascial trigger points in the orofacial region. Moreover, it may be possible that ULF-TENS may provide an

innovative measure against post-operative complications in various scenarios, such as orofacial pain induced by molar extraction in clinical non-invasive interventions.

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