The Effect of Functional Mandibular Shift on the Muscle Spindle Systems in Head-Neck Muscles and the Related Neurotransmitter Histamine

Bing-Li Du, MD, * Jiang-Ning Li, DDS, PhD, † Hong-Ming Guo, DDS, PhD, * Song Li, DDS, PhD, * and Biao Liu, DDS, PhD *

Abstract: The aim of this study is to explore the effects of abnormal occlusion and functional recovery caused by functional mandible deviation on the head and neck muscles and muscle spindle sensory-motor system by electrophysiological response and endogenous monoamine neurotransmitters’ distribution in the nucleus of the spinal tract. Seven-week-old male Wistar rats were randomly divided into 7 groups: normal control group, 2W experimental control group, 2W functional mandible deviation group, 2W functional mandible deviation recovery group, 4W experimental control group, 4W functional mandible deviation group, 4W functional mandible deviation recovery group. Chewing muscles, digastric muscle, splenius, and trapezius muscle spindles electrophysiological response activities at the opening and closing state were recorded. And then the chewing muscles, digastric, splenius, trapezius, and neck trigeminal nucleus were taken for histidine decarboxylase (HDC) detection by high performance liquid chromatography (HPLC), immunofluorescence, and reverse-transcription polymerase chain reaction (RT-PCR). Histamine receptor proteins in the neck nucleus of the spinal tract were also examined by immunofluorescence and RT-PCR. Electromyography activity of chewing muscles, digastric, and splenius muscle was significantly asymmetric; the abnormal muscle electromyography activity was mainly detected at the ipsilateral side. After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle and splenius decreased, muscle excitation weakened, modulation depth decreased, and the muscle spindle afferent impulses of excitation transmission speed slowed down. Changes for digastric muscle electrical activity were contrary. The functions recovered at different extents after removing the deflector. However, trapezius in all the experimental groups and recovery groups exhibited bilateral symmetry electrophysiological responses, and no significant difference compared with the control group. After functional mandibular deviation, HDC protein and messenger ribonucleic acid (mRNA) levels on the ipsilateral sides of the chewing muscle and splenius increased significantly. HDC level changes for digastric muscle were contrary. After the removal of the mandibular position deflector, HDC protein and mRNA levels decreased on the ipsilateral sides of the chewing muscle and splenius while they increased in the digastric muscle. The difference of histamine decarboxylase content in the bilateral trapezius in each experimental group was small. After functional mandibular deviation, the temporomandibular joint mechanical receptors not only caused the fusimotor fiber hypoallergenic fatigue slow response on the ipsilateral sides of splenius, but also increased the injury neurotransmitter histamine release. The authors’ results further support the opinion that the temporomandibular joint receptors may be involved in the mechanical theory of the head and neck muscles nervous system regulation.

Key Words: Functional mandible deviation, fusimotor fiber, histamine decarboxylase, neck trigeminal nucleus

Mandibular asymmetry is a common finding in people with normal facial appearance. However, severe asymmetry may create functional abnormality and esthetic concerns. Recent observations in people with concomitant mandibular suggest a close functional relationship between the head-neck motor systems and the mandibular. Previous researches on neck and stomatognathic system relationship focused on the following points: “Functional jaw movements” are the result of jaw and neck muscles activation, leading to simultaneous movements in the at lanto-occipital, temporomandibular, and the cervical spine joints. Functional mandibular displacement caused by unilateral posterior cross bite could cause mandibular asymmetry. A few studies have studied the morphological changes in the temporomandibular joint (TMJ), including smaller superior condylar space, smaller condylar head, and steeper eminence on the shifted side in asymmetric patients. Other studies also suggested that there was a higher incidence of
The aim of this study is to explore the effects of abnormal occlusion and functional recovery caused by functional mandible deviation on the head and neck muscles, muscle spindle sensory-motor system electrophysiological response and endogenous monoamine neurotransmitters’ distribution in the central nucleus. This study could also provide neurophysiological mechanisms for occlusion of head and neck disorders caused by stomatognathic system dysfunction. What is more, our study offers a theoretical basis for experimental basis for the method of clinical orthodontic correction of mandibular asymmetry in rats.

METHODS

Animal Preparation

All study protocols were approved by the Animal Testing Committee Guidelines at the Capital Medical University. Animal care and handling procedures were in accordance with Guiding Principles for the Care and Use of Animals in the Capital Medical University, China. Sixty seven-week-old male Wistar rats (180g ± 16 g) were randomly divided into 7 groups: Normal control group (NC, n = 10), 2W functional mandible deviation group (2W-FMD, n = 10), 4W functional mandible deviation group (4W-FMD, n = 10), 2W functional mandible deviation recovery group (2W-FMD-R, n = 10), 4W functional mandible deviation recovery group (4W-FMD-R, n = 10). Functional mandible deviation device consisted of 2 parts: upper induction device: 3-dimensional design of the plate stack wax casting device reinforcing glass ionomer cement bonded to the corresponding upper and lower incisors in rats.

Stimulation and Recording

In all experiments, the animals were anesthetized with thiamylal sodium (60 mg/kg i.p.). A supplemental injection of 5 mg/kg i.p. was given when necessary. We monitored the level of anesthesia by checking the animals’ pupil size, flexion and corneal reflexes, and heart rate. The animals were placed in left lateral decubitus with their heads fixed to a stereotaxic frame (models RA-4 and SR-50, Narishige Scientific Instruments, Tokyo, Japan). To stimulate the masseter muscle, we fixed 1 end of a piece of cotton thread to the animals’ lower incisors and the other end to an automatic pulling machine (modified from an artificial respirator, model SN-480-7, Shinano Manufactory, Tokyo, Japan) and applied cyclic sinusoidal stretches. The maximum jaw-opening distance was set at 5.0 mm, with a cycle duration of 4.0 seconds (jaw opening and closing time of 2.0 seconds, followed by an interval of 2.0 seconds). We performed at least 5 trials for stimulation in each unit. Stretch responses of spindle endings were recorded from the fine filament of the masseteric nerve on the right side. We accessed the masseteric nerve after removing the temporalis muscle, and then tied the nerve with a piece of cotton thread, cut at the central end from the tying point. The nerve bundle was then divided into several filaments. We used a silver hook electrode (diameter, 0.7 mm) to record functional single-unit responses. The recording activity belonged to muscle spindle but not to any other receptor system. Chewing muscles, digastric muscle, splenius, and trapezius muscle spindles electrophysiological response activities at the opening and closing state under general anesthesia state were recorded by the Model 1800-type microelectrode amplifier (Dongle Nature Genetics Life Sciences).

All data were captured by means of a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK) and were stored in a computer hard disc. The data were later analyzed offline with the Spike2 software for Windows, Version 4.02a (Cambridge Electronic Design, Cambridge, UK). After the electrophysiological testing, the rats were sacrificed and the chewing muscles, digastric, splenius, trapezius, and neck trigeminal nucleus were taken for HDC detection by high performance liquid chromatography (HPLC), immunofluorescence, and reverse-transcription polymerase chain reaction (RT-PCR). Histamine receptor proteins in the neck trigeminal nucleus were also examined by immunofluorescence and RT-PCR.

High-Performance Liquid Chromatography Analyses

A Waters 600E multisolvent delivery system with a Waters U6K injector was used for HPLC analysis. The system was operated at room temperature. HPLC analyses were done on a Cosmosil 5SL column (4.6 mm I.D. x 150 mm, Nacalai, San Diego, CA) with a solvent system of a mixture of CHCl3/N,N-dimethylformamide/H2O (210:90:4) containing 0.4% acetic acid. The flow rate was at 0.8 mL/min, and monitored at 423 nm.

Immunofluorescence Assay

The tissue sections were prepared for the assay of immunofluorescence as described previously. Serial cross sections of the muscle tissues were generated on a cryostatat 20 micron thickness (Microm, Heidelberg, Germany). Briefly, after the preparation of cell slides by blocking of endogenous peroxidase activity and nonspecific binding sites. The tissues were washed and incubated with normal goat serum for 2 hours at room temperature. Thereafter, anti-histidine decarboxylase antibody (ab37291) and Anti-HRH1 antibody (ab154158) were used as primary antibodies. The tissues were incubated at 4°C overnight. After washing again, the secondary antibodies (Anti-rabbit IgG (H+L), F(ab')2 Fragment (Alexa Fluor 488 Conjugate) #4412, Cell Signaling Technology Inc, Danvers, MA) were applied according to the instruction and tissues were incubated at 4°C overnight. They were then rinsed with PBS 3 times for 10 minutes each. 250 μL DRAQ5 (DRAQ5 #4084, 1:5000, Cell Signaling Technology Inc, CST®#4084) was applied on the slides to stain the nuclear. Finally, the sections were mounted with FluorSave (Calbiochem, La Jolla, CA) mounting reagent. Images of histological sections were collected using Northern Eclipse software (Empix Imaging Inc, Mississauga, ON, Canada) on a
The TMJ mechanoreceptors not only affect the neck muscles’ motor unit activities, but also are concerned in the regulation of postural control of the head. Electromyography activity of chewing muscles was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side. (A–F) Changes for digastric muscle electrical activity were contrary compared with the chewing muscle. Electromyography activity of digastric muscle was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side. (C–J) The weight of casting deflection device had no effect on the threshold, peak instant spike frequencies, and average discharge rate or modulation depth. (G) After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle decreased, (H) muscle excitement weakened (I) the muscle spindle afferent impulses of excitation transmission speed slowed down, and (J) modulation depth decreased. (K–N) The functions recovered at different extent after removing the deflector.

RESULTS

Electromyography Activity of Chewing Muscles Induced by Functional Mandibular Deviation

FIGURE 1. Electromyography (EMG) activity of chewing muscles induced by functional mandibular deviation. (A, B) Electromyography activity of chewing muscles was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side. (C–F) The weight of casting deflection device had no effect on the threshold, peak instant spike frequencies, and average discharge rate or modulation depth. (G) After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle decreased, (H) muscle excitement weakened (I) the muscle spindle afferent impulses of excitation transmission speed slowed down, and (J) modulation depth decreased. (K–N) The functions recovered at different extent after removing the deflector.

FIGURE 2. Electromyography (EMG) activity of digastric muscle induced by functional mandibular deviation. (A, B) Changes for digastric muscle electrical activity were contrary compared with the chewing muscle. Electromyography activity of digastric muscle was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side. (C–J) The weight of casting deflection device had no effect on the threshold, peak instant spike frequencies, and average discharge rate or modulation depth. (G) After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle increased, (H) muscle excitement increased (I) the muscle spindle afferent impulses of excitation transmission speed accelerated, and (J) modulation depth increased. And the changes above increased with time. (K–N) The functions recovered at different extent after removing the deflector.

Statistical Analysis

Statistical analysis was performed with SPSS17.0 statistical software. Comparison between the groups used Student t test or 1-way analysis of variance. The difference was considered significantly if $P < 0.05$, * means $P < 0.05$, ** means $P < 0.01$, and *** means $P < 0.001$. 

© 2017 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.
Electromyography Activity of Digastric Muscle Induced by Functional Mandibular Deviation

Changes for digastic muscle electrical activity were contrary compared with the chewing muscle. Electromyography activity of digastic muscle was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side (Fig. 2A and B). The weight of casting deflection device had no effect on the threshold (Fig. 2C), peak instant spike frequencies (Fig. 2D), and average discharge rate (Fig. 2E) or modulation depth (Fig. 2F). After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle increased (the threshold for 2W-EC group was 394.08 ± 19.15 mN, the threshold for 2W-FMD was 315.23 ± 16.39 mN, P < 0.05; the threshold for 4W-EC group was 394.22 ± 18.76 mN, the threshold for 4W-FMD was 284.77 ± 18.82 mN, P < 0.05) (Fig. 2G), muscle excitement increased (the peak instant spike frequency for 2W-EC group was 40.24 ± 7.50 Hz, for 2W-FMD was 53.87 ± 6.62 Hz, P < 0.05; the peak instant spike frequency for 4W-EC group was 38.58 ± 10.93 Hz, for 4W-FMD was 69.11 ± 7.29 Hz, P < 0.05) (Fig. 2H), the muscle spindle afferent impulses of excitation transmission speed slowed down (Fig. 2I), and modulation depth decreased (Fig. 2J). And the changes above increased with time. The functions recovered at different extents after removing the deflector (Fig. 2K–N).

Electromyography Activity of Splenius Muscle Induced by Functional Mandibular Deviation

Changes for splenius muscle electrical activity were similar with the chewing muscle. Electromyography activity of splenius muscle was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side (Fig. 3A and B). The weight of casting deflection device had no effect on the threshold (Fig. 3C), peak instant spike frequencies (Fig. 3D), and average discharge rate (Fig. 3E) or modulation depth (Fig. 3F). After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle decreased (Fig. 3G), muscle excitement weakened (Fig. 3H), the muscle spindle afferent impulses of excitation transmission speed slowed down (Fig. 3I), and modulation depth decreased (Fig. 3J). And the changes above increased with time. The functions recovered at different extents after removing the deflector (Fig. 3K–N).

Electromyography Activity of Trapezius Muscle Induced by Functional Mandibular Deviation

However, trapezius in all the experimental groups and recovery groups exhibited bilateral symmetry electrophysiological responses, and no significant difference compared with the control group (Fig. 4).

Histidine Decarboxylase Levels in the Chewing Muscles

Histidine decarboxylase level of chewing muscles was significantly asymmetric; the abnormal muscle HDC expression was mainly detected at the ipsilateral side (Fig. 5A and B). After functional mandibular deviation, HDC protein levels (2W-FMD versus 2W-EC, 128.96 ± 6.91 ng/g versus 105.56 ± 14.70 ng/g, P < 0.05; 4W-FMD versus 4W-EC, 143.42 ± 6.57 ng/g versus 112.18 ± 12.71 ng/g, P < 0.05) on the ipsilateral sides of the muscle.
Histidine decarboxylase levels in the chewing muscles. (A, B) While chewing muscle increased significantly. After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the chewing muscle (4W-FMD versus 4W-EC, 12.48 ng/g versus 16.90 ng/g, P < 0.05). (C) After functional mandibular deviation, HDC protein levels increased on the ipsilateral sides of the chewing muscle increased significantly. After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the chewing muscle (2W-FMD versus 2W-EC, 117.50 ± 7.71 ng/g versus 129.36 ± 16.90 ng/g, P < 0.05; 4W-FMD versus 4W-EC, 102.77 ± 6.81 ng/g versus 130.38 ± 12.48 ng/g, P < 0.05). After the removal of the mandibular position deflector, the detection indicators above decreased at different extents. After the removal of the mandibular position deflector, neither HDC protein levels nor HDC mRNA levels changed compared with the control group.

Histidine Decarboxylase Levels in the Digastric Muscle

Histidine decarboxylase levels in the digastric muscle were contrary. Histidine decarboxylase level of digastric muscle was significantly asymmetric; the abnormal muscle HDC expression was mainly detected at the ipsilateral side (Fig. 6A and B). After functional mandibular deviation, HDC protein levels on the ipsilateral sides of the digastric muscle decreased significantly (2W-FMD versus 2W-EC, 117.50 ± 7.71 ng/g versus 129.36 ± 16.90 ng/g, P < 0.05; 4W-FMD versus 4W-EC, 102.77 ± 6.81 ng/g versus 130.38 ± 12.48 ng/g, P < 0.05) on the ipsilateral sides of the digastric muscle increased significantly. After the removal of the mandibular position deflector, HDC protein levels increased on the ipsilateral sides of the digastric muscle (4W-FMD versus 4W-EC, 117.79 ± 9.83 ng/g versus 102.77 ± 6.81 ng/g, P < 0.05) (Fig. 6C). The HDC mRNA level change was coincident with the protein change (Fig. 6D).

Histidine Decarboxylase Levels in the Splenius Muscle

Histidine decarboxylase level of splenius muscle was significantly asymmetric; the abnormal muscle HDC expression was mainly detected at the ipsilateral side (Fig. 7A and B). After functional mandibular deviation, HDC protein levels (2W-FMD versus 2W-EC, 110.13 ± 11.61 ng/g versus 91.91 ± 12.16 ng/g, P < 0.05; 4W-FMD versus 4W-EC, 132.04 ± 8.64 ng/g versus 91.86 ± 15.33 ng/g, P < 0.05) on the ipsilateral sides of the Splenius muscle increased significantly. After the removal of the mandibular position deflector, HDC protein levels decreased...
The effects of different types of stress on the ipsilateral sides of the trigeminal nucleus increased significantly. After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the trigeminal nucleus. (B) The HDC mRNA level change was coincident with the protein change. (C) After functional mandibular deviation, histamine receptor protein levels on the ipsilateral sides of the trigeminal nucleus increased significantly. After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the trigeminal nucleus. (D) And histamine receptor mRNA level change was coincident with the protein change. HAD, histamine decarboxylase.

on the ipsilateral sides of the Splenius muscle (4W-FMD-R versus 4W-FMD, 115.01 ± 8.22 ng/g versus 132.04 ± 8.64 ng/g, P < 0.05) (Fig. 7C). The HDC mRNA level change was coincident with the protein change (Fig. 7D).

Histidin Decarboxylase Levels in the Trapezius Muscle

The difference of histamine decarboxylase content in the bilateral trapezius in each experimental group was small. Trapezius in all the experimental groups and recovery groups exhibited bilateral symmetry HDC expression, and no significant difference (Fig. 8A and B). After the removal of the mandibular position deflector, the detection indicators above decreased at different extents. After the removal of the mandibular position deflector, neither HDC protein levels (Fig. 8C) nor HDC mRNA levels (Fig. 8D) changed compared with the control group.

Neck Monoamine Neurotransmitter Histamine Release Test Results in the Trigeminal Nucleus

After functional mandibular deviation, HDC protein levels on the ipsilateral sides of the trigeminal nucleus increased significantly (2W-FMD versus 2W-EC, 2.132 ± 0.256 versus 1.013 ± 0.060, P < 0.05; 4W-FMD versus 4W-EC, 2.480 ± 0.301 versus 1.007 ± 0.078, P < 0.05). After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the trigeminal nucleus (2W-FMD-R versus 2W-FMD, 1.543 ± 0.042 versus 2.132 ± 0.256, P < 0.05; 4W-FMD-R versus 4W-FMD, 1.793 ± 0.234 versus 2.480 ± 0.301, P < 0.05) (Fig. 9A). The HDC mRNA level change was coincident with the protein change (Fig. 9B). After functional mandibular deviation, histamine receptor protein levels on the ipsilateral sides of the trigeminal nucleus increased significantly (2W-FMD versus 2W-EC, 1.783 ± 0.103 versus 0.960 ± 0.080, P < 0.05; 4W-FMD versus 4W-EC, 2.311 ± 0.144 versus 1.014 ± 0.081, P < 0.05) (Fig. 9C). After the removal of the mandibular position deflector, HDC protein levels decreased on the ipsilateral sides of the trigeminal nucleus (2W-FMD-R versus 2W-FMD, 1.292 ± 0.193 versus 1.783 ± 0.103, P < 0.05; 4W-FMD-R versus 4W-FMD, 1.857 ± 0.268 versus 2.311 ± 0.144, P < 0.05). And histamine receptor mRNA level change was coincident with the protein change (Fig. 9D).

DISCUSSION

The control of jaw movements and position is performed by inputs from low-threshold mechanoreceptors located throughout the orofacial region. These include periodontal and mucosal mechanoreceptors and muscle spindles.12 A change in head position was observed at the beginning of the first jaw-movement cycle, and this adjusted head position was maintained during the following cycles. In addition to the prevailing head extension, the maximal jaw-open/-closing cycles were paralleled by head extension-flexion movements.19 It is important to assess the morphology and function of the neck muscles and cervical spine prior to occlusal therapy in patients with asymmetric TMJ structures.19 Functional shift of rat mandible changes the morphology of the condylar cartilage in the lateral region on the ipsilateral side.20

Electromyography activity of chewing muscles, digastra, and splenius muscle was significantly asymmetric; the abnormal muscle EMG activity was mainly detected at the ipsilateral side. After functional mandibular deviation, muscle sensitivity on the ipsilateral sides of the chewing muscle and splenius decreased, muscle excitation weakened, modulation depth decreased, and the muscle spindle afferent impulses of excitation transmission speed slowed down. And the changes above increased with time. Changes for digastric muscle electrical activity were contrary. The functions recovered at different extents after removing the deflector. In the trigeminal somatosensory system, there are various receptors on the orofacial structures, for example, mechanoreceptors in the tooth, periodontium, oral mucosa, and TMJ. All of them are potential candidates for modulators of the neck motor system. Recently, it was observed that periodontal mechanical stimulation could elicit reflex responses in neck muscles by.21 During growth on the functional characteristics of TMJ mechanoreceptors, the threshold of the TMJ units was significantly lower in the experimental group than in the control group.22 Both mandibular positions tested decreased the EMG activity of the masticatory and cervical muscles in the relaxed and full bite positions.23 The innervations of the TMJ by somatosensory and sympathetic fibers suggested that sympathetic nerves could be responsible for alodinia or neuropathic pain caused by temporomandibular disorders.24

In our study, after functional mandibular deviation, HDC protein and mRNA levels on the ipsilateral sides of the chewing muscle and splenius increased significantly. HDC level changes for digastric muscle were contrary. After the removal of the mandibular position deflector, HDC protein and mRNA levels decreased on the ipsilateral sides of the chewing muscle and splenius while they increased in the digastric muscle. The difference of histamine decarboxylase content in the bilateral trapezius in each experimental group was small. After functional mandibular deviation, HDC protein, HDC mRNA levels, histamine receptor proteins, and histamine receptor mRNA levels on the ipsilateral sides of the trigeminal nucleus increased significantly. After the removal of the mandibular position deflector, the detection indicators above decreased at different extents. A patient-control designed was used to investigate associations and interactions between muscle activities measured by surface EMG in the upper trapezius muscle and subjectively reported risk factors in workers with and without shoulder and neck pain.25 The effects of different types of stress (water bathing, cold, restraint, and prolonged walking) on HDC activity in masseter were examined in mice. And all of these stresses elevated gastric HDC activity.26

In conclusion, after functional mandibular deviation, the TMJ mechanical receptors not only caused the fusimotor fiber

© 2017 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.
hypoallergenic fatigue slow response on the ipsilateral sides of splenius, but also increased the injury neurotransmitter histamine release. Our results further support the opinion that the temporomandibular joint receptors may be involved in the mechanical theory of the head and neck muscles nervous system regulation.

REFERENCES

1. Ponyi S, Szabo G, Nyilasi J. Asymmetry of mandibular dimensions in European skulls. Proc Finn Dent Soc 1991;87:321–327
2. Athanasou AE, Melsen B, Mavreas D, et al. Stomatognathic function of patients who seek orthognathic surgery to correct dentofacial deformities. Int J Adult Orthod Orthognath Surg 1989;4:239–254
3. Sakaguchi K, Mehta NR, Abdallah EF, et al. Examination of the relationship between mandibular position and body posture. Cranio 2007;25:237–249
4. Eriksson PO, Haggman-Henrikson B, Nordh E, et al. Co-ordinated mandibular and head-neck movements during rhythmic jaw activities in man. J Dent Res 2000;79:1378–1384
5. Pinto AS, Buschang PH, Throckmorton GS, et al. Morphological and positional asymmetries of young children with functional unilateral posterior crossbite. Am J Orthod Dentofacial Orthop 2001;120:513–520
6. Akahane Y, Deguchi T, Hunt NP. Morphology of the temporomandibular joint in skeletal class III symmetrical and asymmetrical cases: a study by cephalometric laminography. J Orthod 2001;28:119–128
7. Goto TK, Nishida S, Nakayama E, et al. Correlation of mandibular deviation with temporomandibular joint MR dimensions, MR disk position, and clinical symptoms. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:743–749
8. Kure-Hattori I, Watari I, Takei M, et al. Effect of functional shift of the mandible on lubrication of the temporomandibular joint. Arch Oral Biol 2012;57:987–994
9. Liu C, Kaneko S, Soma K. Effects of a mandibular lateral shift on the condyle and mandibular bone in growing rats. Angle Orthod 2007;77:787–793
10. de Wijer A, Steenks MH, de Leeuw JR, et al. Symptoms of the cervical spine in temporomandibular and cervical spine disorders. J Oral Rehabil 1996;23:742–750
11. Hunt CC. Mammalian muscle spindle: peripheral mechanisms. Physiol Rev 1990;70:643–663
12. Ayada K, Tadano T, Endo Y. Gnawing behavior of a mouse in a narrow cylinder: a simple system for the study of muscle activity, fatigue, and stress. Physiol Behav 2002;77:161–166
13. Yabushita T, Zeredo JL, Toda K, et al. Role of occlusal vertical dimension in spindle function. J Dent Res 2005;84:245–249
14. Kinoshita E, Saito M. Novel histamine measurement by HPLC analysis used to assay histidine decarboxylase inhibitory activity of shoyuflavones from soy sauce. Biosci Biotechnol Biochem 1998;62:1488–1491
15. Bi Y, Tian M, Le J, et al. Study on the expression of PAK4 and P54 protein in breast cancer. World J Surg Oncol 2016;14:160
16. Jablonska K, Grzegorzka J, Podhorska-Okolow M, et al. Prolactin-induced protein as a potential therapy response marker of adjuvant chemotherapy in breast cancer patients. Am J Cancer Res 2016;6:878–893
17. Kobayashi M, Yabushita T, Zeredo JL, et al. Splenius muscle activities induced by temporomandibular joint stimulation in rats. Brain Res Bull 2007;72:44–48
18. Eriksson PO, Haggman-Henrikson B, Nordh E, et al. Co-ordinated mandibular and head-neck movements during rhythmic jaw activities in man. J Dent Res 2000;79:1378–1384
19. Kondo E. Features and treatment of skeletal class III malocclusion with severe lateral mandibular shift and asymmetric vertical dimension. J Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:743–749
20. Sato C, Muramoto T, Soma K, et al. Functional lateral deviation of the mandible and its positional recovery on the rat condylar cartilage during the growth period. Angle Orthod 2006;76:591–597
21. Widénfalk B, Wiberg M. Origin of sympathetic and sensory innervation of the temporo-mandibular joint. A retrograde axonal tracing study in the rat. Neurosci Lett 1990;109:30–35
22. Ishida T, Yabushita S, Soma K. Functional changes of temporomandibular joint mechanoreceptors induced by reduced masseter muscle activity in growing rats. Angle Orthod 2009;79:978–983
23. Ceneviz C, Mehta NR, Forgione A, et al. The immediate effect of changing mandibular position on the EMG activity of the masseter, temporalis, sternocleidomastoid, and trapezius muscles. Cranio 2006;24:237–244
24. Yoshino K, Kawagishi S, Amano N. Morphological characteristics of primary sensory and post-synaptic sympathetic neurones supplying the temporomandibular joint in the cat. Arch Oral Biol 1998;43:679–686
25. Vasseljen OJ, Westgaard RH. Can stress-related shoulder and neck pain develop independently of muscle activity? Pain 1996;64:221–230
26. Ayada K, Watanabe M, Endo Y. Elevation of histidine decarboxylase activity in skeletal muscles and stomach in mice by stress and exercise. Am J Physiol Regul Integr Comp Physiol 2000;279:R2042–R2047