Archives Italiennes de Biologie, 149: 478-491, 2011.

Masseter EMG activity during sleep and sleep bruxism

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ABSTRACT

The masseter muscle is involved in the complex and coordinated oromotor behaviors such as mastication during wakefulness. The masseter electromyographic (EMG) activity decreases but does not disappear completely during sleep: the EMG activity is generally of low level and inhomogeneous for the duration, amplitude and intervals. The decreased excitability of the masseter motoneurons can be determined by neural substrates for non-rapid eye movement (NREM) and REM sleep. The masseter EMG activity is increased in association with the level of arousal fluctuations within either sleep state. In addition, there are some motor events such as REM twitches, swallowing and rhythmic masticatory muscle activity (RMMA), whose generation might involve the additional activation of specific neural circuits. Sleep bruxism (SB) is characterized by exaggerated occurrence of RMMA. In SB, the rhythmic activation of the masseter muscle can reflect the rhythmic motor inputs to motoneurons through, at least in part, common neural circuits for generating masticatory rhythm under the facilitatory influences of transient arousals. However, it remains elusive as to which neural circuits determine the genesis of sleep bruxism. Based on the available knowledge on the masseter EMG activity during sleep, this review proposes that the variety of the masseter EMG activity patterns during sleep can result from the combinations of the quantitative, spatial and temporal neural factors sending net facilitatory inputs to trigeminal motoneurons under the control of sleep regulatory systems.

Key words

Masseter • Trigeminal motor system • Sleep • Micro-arousal • Sleep bruxism

Introduction

Muscles of the jaw involve simple or complex patterns of jaw movements when we eat, talk, drink, laugh, breath, and smile during wakefulness. When we sleep, most oromotor behaviors such as mastication disappear and the EMG activity of the jaw muscles remains low. However, an increased EMG activity of the jaw-closing (JC) muscles, such as the masseter, can be found in some populations. Such condition can cause orodental problems such as tooth wear and fracture, temporomandibular disorders, headache, and failures of dental prostheses and implants (Lavigne et al., 2003; Kato and Lavigne, 2010). One of the conditions that are more clearly defined is sleep (-related) bruxism (SB). Contrary to the advances of the knowledge for trigeminal motor excitability in sleep, neurophysiological mechanism underlying the genesis of the masseter contractions during sleep remains elusive. This review first gives an overview of masticatory motor system, and then, EMG features of the masseter contractions during sleep in humans and animals. Finally, factors affecting the masseter EMG activity during sleep and a

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characteristic of masseter EMG activity in SB will be discussed.

Masticatory jaw motor system

Muscles of the jaw

Muscles of the jaw are classified into functionally antagonistic groups such as JC and jaw-opening (JO) muscles. The masseter muscle belongs to the JC group together with the temporalis and medial pterygoid muscles. The major role of the JC muscles like the masseter muscle, is to produce adequate masticatory force between the teeth to crush foods (Lund, 1991). In humans, maximal bite force ranges between 400-1110 N when subjects clench their teeth (Van Der Bilt, 2011). The JC muscles can also contribute to the maintenance and/or stabilization of the jaw position (Hollowell and Suratt, 1991; Woda et al., 2001). The lateral pterygoid muscle is activated for lateral and protrusive jaw movements (Murray et al., 2001). The JO muscles including the digastric and mylohyoid muscles do not actually produce forceful contraction but they are activated in jaw-opening movements and for stabilizing the position of the jaw and the hyoid bone (e.g., swallowing) by counteracting the contractions of JC muscles.

Trigeminal motoneurons and premotoneurons

The muscles of the jaw are innervated by trigeminal motoneurons located in the trigeminal motor nucleus (Vmo) in the rostral part of pons. Dorsolateral part of the Vmo contains the motoneurons for the JC muscles and the lateral pterygoid while ventromedial part of the Vmo contains motoneurons for the JO muscles. A half of synaptic boutons onto trigeminal motoneurons are excitatory type (glutamate-immunopositive) and the other half contains three types of inhibitory boutons (glycine, GABA, and both) (Shigenaga et al., 2007); the excitatory influences in proportion to inhibitory ones are likely higher compared to spinal motoneurons (35% excitatory and 59% inhibitory) probably because of a lack of reciprocal or Renshaw inhibitions in the trigeminal motor system (Lund, 1991).

The excitatory and inhibitory inputs onto trigeminal motoneurons are coming from premotoneurons (e.g., last-order interneurons) located in the areas surrounding the Vmo as well as the midbrain, pons and medulla (Lund, 1991; Lund et al., 1998). Premotoneurons located lateral to Vmo mainly project to the JC motoneurons (e.g., intertrigeminal region and principal trigeminal sensory nucleus), while those located mediovental to Vmo project mainly to the JO motoneurons (Yoshida et al., 2009). Other premotoneurons project to both JC and JO motoneurons: they are located in the parabrachial and supratrigeminal nuclei, parvocellular reticular nucleus pars alpha, rostral part of trigeminal spinal nucleus, and juxtatrigeminal region (Yoshida et al., 2009). Glutamatergic, GABAergic, and glycinergic neusons are intermingled within the above premotoneurons (Turman and Chandler, 1994a, 1994b; Kolta et al., 2000). These premotoneurons have the connections to other cranial motor nulei and ipsilateral/bilateral connections to other premotoneurons (Lund, 1991; Lund et al., 1998). GABAergic and glycinergic neurons in the medial reticular formation, such as caudal pontine reticular nucleus, paragigantocelluar reticular nucleus and gigantocellular reticular nucleus also project to trigeminal premotoneurons (Rampon et al., 1996; Kolta et al., 2000). Monoaminergic neurons that contain serotonin (e.g., raphe nuclei) and noradrenaline (e.g., locus subceruleus) project to trigeminal motoneurons (Fort et al., 1990). Medullary serotonergic neurons have more potent projection to the JC than the JO motoneurons (Nagase et al., 1997). Direct projections from the lateral hypothalamus, and central nucleus of the amygdala to trigeminal motoneurons and premotoneurons have been also reported (Mascaro et al., 2009). Muscle spindle afferents in trigeminal mesencephalic nucleus project to the JC motoneurons: these mediate the monosynaptic masseteric reflex (Lund, 1991).

Masticatory motor controls

During rhythmic oromotor behaviors such as mastication, neurons in the medial reticular formation generate basic masticatory rhythm, and, based on the generated rhythm, trigeminal premotoneurons lateral to the Vmo generate the final motor inputs to trigeminal motoneurons by integrating descending commands and sensory inputs (Nakamura and Katakura, 1995; Lund et al., 1998).

Masticatory sequence

Mastication is characterized by a sequence of rhythmic jaw movements produced by the alternative activation of the JC and JO muscles (Fig. 1A) (Lund, 1991; Masuda et al., 1997). After foods are ingested, repetitive or rhythmic JO muscle contractions are associated with vertical open-close jaw movements (Fig. 1B). While chewing foods between molar teeth, JC and JO muscles are alternatively activated in relation to rhythmic jaw movements (RJMs) (Fig. 1A). The jaw moves medially from the chewing side when the foods are ground between upper and lower molar teeth (Fig. 1C): JC muscles are most activated for masticatory force production (Hidaka et al., 1997; Van Der Bilt, 2011). During mastication, muscles of the tongue (innervated by hypoglossal motoneurons), cheeks and lips (innervated by facial motoneurons) exhibit highly coordinated patterns of activities with JC and JO muscles. Then, masticatory sequence is finished with swallowing (Lund, 1991) (Fig. 1D).

Descending commands

Unlike other rhythmic movements, such as respiration and locomotion, in many species, the rhythmic jaw movements are known to be induced by repetitive electrical stimulation (30-50 Hz) to the face area of sensorimotor cortex, the basal ganglia, lateral hypothalamus, amygdala and midbrain reticular formation (Kawamura and Tsukamoto, 1960; Hashimoto et al., 1989; Liu et al., 1993). The patterns of the induced RJMs depend on the site of stimulation (Liu et al., 1993). Since repetitive stimulation is required for inducing RJMs, a summation of excitatory and/or inhibitory influences within the brainstem neural networks can be a significant factor for the generation of the rhythmic patterns. When several types of RJMs are cortically induced in animals, most premotoneurons in parovocellular reticular nucleus and rostral part of trigeminal spinal nucleus are phasically active in the distinct phases within a cycle of trigeminal motoneuron discharge (Lund et al., 1998). However, some neurons are activated for a single pattern of the cortically induced RJMs while others are activated for multiple patterns (Lund et al., 1998). Several distinct descending projections from cortical or subcortical structures to trigeminal premotoneurons consist of multiple pathways, which can also contribute to the organization of the spatial and temporal patterns for the generation of distinct patterns of rhythmic jaw motor activity (Mascaro et al. 2009; Yoshida et al. 2009; Iida et al., 2010).

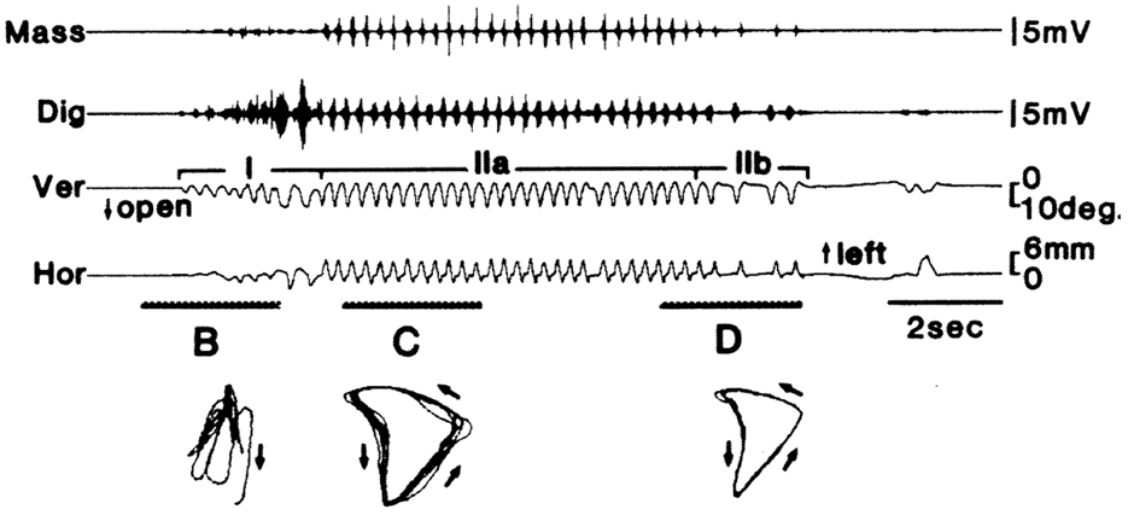

Fig. 1. - Patterns of the jaw muscle electromyographic (EMG) activities and jaw movements during masticatory sequence in an awake head-restraint rabbit. After a pellet was put into the mouth, it was transported to the molar teeth (I), chewed (IIa) and prepared for swallowing (IIb). Masseter muscle (Mass) is rhythmically active during chewing and it is alternatively activated with the digastric muscle (Dig). Ver and Hor: vertical and horizontal jaw movements. Bottom traces: jaw movements on the frontal plane during transportation (I), chewing (IIa) and preswallowing periods (IIb). Small arrows: direction of jaw movements. (Modified from Masuda et al., 1997 and reproduced with permission of the American Physiological Society).

Peripheral feedback

Peripheral feedbacks from muscle spindle and periodontal afferents modify the rhythmic outputs from premotor circuits onto trigeminal motoneurons, since the activity and duration of the masseter EMG bursts and the lateral jaw excursion increase in proportion to the increment of masticatory force (Fig. 2) (Lavigne et al., 1987; Hidaka et al., 1997). Muscle spindle afferents are more responsible for the force-dependent facilitation of the JC muscles while periodontal afferents for the quick build-up of masticatory force when the teeth are loaded (Hidaka et al., 1997). However, periodontal afferents also play an important role in protecting oral structures from damage (e.g., tooth fracture, oral mucosa biting) by initiating the jaw opening reflex (Lund, 1991). Periodontal and muscle spindle afferents in trigeminal mesencephalic nucleus receive abundant innervation from cortical and subcortical structures (Mascaro et al., 2009; Iida et al., 2010). However, the modulatory influences of oromotor functions by descending projections remain to be clarified.

Inhomogeneous masseter EMG activity during sleep

In humans

Several studies documenting the overall changes of masseter EMG activity during sleep and wakefulness were done using ambulatory surface EMG recordings in humans. In these studies, the amplitude of the masseter EMG bursts is normalized by that during maximal voluntary tooth clenching task (%MVC). The masseter EMG bursts were detected based on the pre-defined EMG threshold (e.g., 20%MVC) and analyzed to estimate how frequently and strongly the masseter muscle is activated during the presumably sleeping period.

In young adults, masseter EMG bursts with the amplitude higher than 25%MVC were found to occur at 30-50 bursts/min during eating (Miyamoto et al., 1996). During non-eating wakefulness, the bursts occurred at 2 to 5 times/min and the majority of them were of low amplitude < 25%MVC (Kato et al. 2006; Miyamoto et al. 1996). Approximately 80% of bursts were of short duration (< 2 s) and a half of the bursts were associated with non-nutritive swallowing (Kato et al. 2006). During sleep, the number of masseter EMG bursts further decreased from non-eating waking time (Miyamoto et al., 1996), but the amplitude of most bursts was at around 10-20% of MVC (Ikeda et al. 1996; Gallo et al., 1999). However, the masseter can occasionally exhibit the EMG activity exceeding that during maximal voluntary clenching (Clarke and Townsend, 1984). The duration of the bursts was variable but 42% of them lasted around 0.5 s (Gallo et al., 1999). Masseter EMG activations can occur unevenly during sleep period (Gallo et al., 1999). There are periods with frequent masseter EMG bursts or jaw closing movements and these periods are likely to be repeated approximately every 90-120 min during the night (Powell and Zander, 1965). The clustering of masseter bursts can emerge more clearly in subjects exhibiting high number of masseter EMG bursts (e.g., sleep bruxism) within the sleep cycle (Huynh et al., 2006a).

In animals

In freely moving animals, the EMG activities of the masseter muscle have been shown to be highly variable during wakefulness (Kato et al. 2007a; Kato et al. 2010). High EMG activity is related to the presence of chewing and drinking behaviors. In the guinea pig, in comparison to average integrated EMG activity during wakefulness, the masseter EMG activity is decreased by 70-80% during sleep period (Kato et al. 2007a; Kato et al. 2010). The level of masseter EMG activity varies during sleep because of the inhomogeneous characteristics of the masseter EMG bursts. In a pilot analysis, burst duration and activity were up to three times more variable during NREM sleep than REM sleep; mean values of burst duration and activity were higher during NREM sleep than REM sleep; during REM sleep, the bursts with a short duration and low activity (REM twitches) occur (Kato et al. 2007b; Anaclet et al. 2010). A decrease of the EMG activity levels for the masseter and the digastric muscles from NREM to REM sleep is not evident (Kato et al., 2010). The masseter muscle exhibits a higher EMG activity level than the digastric, and the variability of the masseter EMG activity is larger than those of the digastric (Kato et al., 2010). Moreover, the two muscles are not always activated equivalently and synchronously. These suggest that distinct premotor modulations of facilitatory and inhibitory

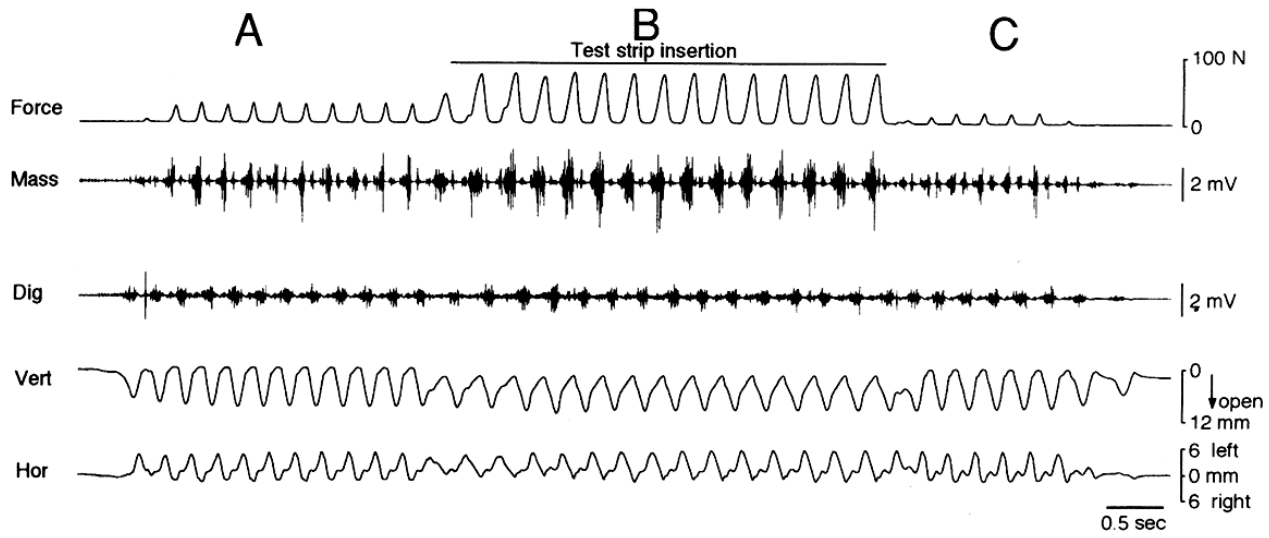

Fig. 2. - Changes in jaw muscle EMG activities and jaw movements in relation to the intensity of the cortically induced rhythmic chewing in a rabbit. When test strip was applied between upper and lower molar teeth (indicated by B), masticatory force (Force) increased simultaneously with the increase in the amplitude and duration of the masseter (Mass) EMG bursts while the digastric (Dig) EMG bursts did not change. The masticatory rhythm became slower during strip application as seen in the vertical (Vert) and horizontal (Hor) components of the jaw movements. (Reprinted from Hidaka et al., 1997 with permission of the American Physiological Society).

influences may generate the inhomogeneous nature of the masseter and digastric EMG bursts, as well as a heterogeneous distribution of facilitatory influences onto motoneurons of the two muscles during NREM and REM sleep. However, the probability of both muscles being highly activated around the same time can increase in relation to the intensity of transient arousals from NREM sleep; such arousal-dependency was not evident during REM sleep (Kato et al., 2010).

Motor excitability and muscle tone in sleep

Transition from wakefulness to sleep is related to a reduction of motility and motor excitability. Changes in the EMG tone from wakefulness to sleep have been reported for muscles of the jaw, face, tongue, limb and body. The changes in the muscle tone are linked to motoneuronal excitability controlled by neurophysiological substrates regulating NREM and REM sleep.

During NREM sleep, noradrenergic and serotonergic neurons, the firing of which is linked to jaw motor activity (e.g., chewing) during wakefulness, exhibit a decreased and irregular firing compared to wakefulness (Aston-Jones et al., 1991; Jacobs et al., 2002). Additionally, neural activities of other brain regions that can modulate motor activity and movements (e.g., motor cortex) decrease (Evarts, 1964; Marchiafava and Pompeiano, 1964). A reduction of descending excitatory influences from forebrain and brainstem structures to motoneurons leads to a decline of jaw muscle tone, characterized by a modest reduction of the membrane potential of the trigeminal motoneurons for the the masseter and digastirc muscles (Chandler et al., 1980; Burgess et al., 2008). The amplitude of jaw opening reflex and monosynaptic masseteric reflex were found not to clearly decrease during NREM sleep compared to wakefulness (Chase, 1971; Inoue et al., 1999) because the excitability of primary afferents and neurons in reflex circuits (e.g., trigeminal sensory nuclei) does not decrease much (Cairns et al., 1995, 1996).

During REM sleep, the excitability of trigeminal motoneurons is decreased by postsynaptic inhibition exerted by glycinergic neurons located in the ventromedial medulla (Chase, 2008; Soja, 2008). A recent study has proposed that there is a contribution of GABAergic inhibition onto trigeminal motoneurons (Brooks and Peever, 2008). In addition, disfa-

cilitation of motoneurons has been reported in other cranial motoneurons (Funk, 2008; Kubin, 2008). Whether all motoneurons are equally inhibited during REM sleep has not been clarified (Funk, 2008). Under such inhibitory processes, the masseter and digastric motoneurons, as well as lumbar motoneurons, are hyperpolarized (Morales and Chase, 1978; Nakamura et al., 1978; Pedroarena et al., 1994). Both JOR and MMR activities are strongly suppressed during REM sleep compared to NREM sleep (Chase, 1971; Inoue et al., 1999). Nonetheless, there is a 'phasic REM sleep' period in which phasic muscular twitches occur in jaw muscles during REM sleep, especially in rodents (Anaclet et al., 2010).

Studies with visual and quantitative estimations of EMG activity showed that the decrease of muscle tone from NREM to REM sleep is clear for postural and suprahyoid muscles (e.g., the digastric and mylohyiod) while there are only minor changes in EMG activity in the masseter and other muscles of the head, neck, limb or trunk in humans (Jacobson et al., 1964; Kato et al., 2003; Okura et al., 2006). In animals, postural neck muscles showed a large diminution of muscle tone from NREM to REM sleep in comparison to the masseter (Kato et al., 2007a). Inter-muscle difference in the modulation of muscle tone can be related to the neuromodulatory influences that meet the physiological demands during sleep (e.g., respiration) (Hollowell and Suratt, 1991; Fenik et al., 2005).

Facilitation of muscle activity in sleep

Transient arousal

In both humans and animals, masseter activation during sleep is mainly of transient nature. Within a given sleep stage, various transient and phasic physiologic events occur (Halasz et al., 2004). Transient arousals, such as micro-arousals, occur frequently during sleep in humans and animals (Quattrochi et al., 2000; Halasz et al., 2004). Micro-arousals are associated with a shift of EEG activity towards desynchronized pattern for 10-15 s and a brief increase of the heart rate. In humans, micro-arousals more frequently occur at the end of a NREM period in relation to phases A2 and A3 of the cyclic alternating pattern (Halasz et al., 2004). Transient arousal can be induced by exogenous (e.g., sound) or endogenous (e.g., blood pressure) stimulation. The responsiveness of transient arousals to sensory stimulation differs between sleep stages and with the modalities of stimuli (Kato et al., 2004; Lavigne et al., 2004). Transient arousal period from sleep has been suggested as a state of sensory and motor functions that are distinct from complete wakefulness (Horner et al., 1997). Cortical EEG shift in response to sensory stimuli is associated with the increased neural discharge in the monoaminergic system (e.g., locus ceruleus and raphe nuclei) (Leung and Mason, 1999; Sakai and Crochet, 2001; Takahashi et al., 2010). Thus, transient arousal is an intermediate state in which the ascending activating systems responsible for waking cortical and cardiac activity are activated but insufficient to produce wakefulness (Horner et al., 1997; Leung and Mason, 1999; Halasz et al., 2004; Foo and Mason, 2005).

Hierarchical activation of the masseter

Motor activations or movements are frequently associated with transient arousals (Halasz et al., 2004). In humans, the masseter and suprahyoid muscle tone are increased when transient cortical EEG arousals are induced by sensory stimulation during NREM sleep (Kato et al., 2003; Kato et al., 2004), suggesting the reactivation of facilitatory influences (Leung and Mason, 1999; Burgess et al., 2008). However, no muscle tone was observed during cortical EEG shift (e.g., alpha activity) triggered during REM sleep. These suggest a stage-dependent difference in the threshold for motor activation related to arousals (Kato et al., 2004). In addition, the high intensity of the masseter and the digastric EMG activations is correlated to the high level (intensity) of transient arousals (e.g., more desynchronized cortical activity) in animals (Kato et al., 2010). The intensity of muscle activity in a single muscle represents an increase of net facilitatory influences through premotor pathways onto a given muscle. Moreover, as the level of arousal is increased towards awakening, more muscles in the jaw and body are activated during NREM and REM sleep and motor activation becomes more intense (e.g., movements) (Kato et al., 2004; Lavigne et al., 2004; Kato et al., 2010). These suggest that the increased influences of ascending reticular activation may expand to larger areas of the central nervous system that provide the descending facilitatory influences onto motoneurons at multiple levels.

Phasic activation during REM sleep

On the background of tonic motor inhibition during REM sleep, phasic muscle twitches of the jaw and tongue muscles can occur in animals (Lu et al., 2005; Kato et al., 2007a; Anaclet et al., 2010). In humans, facial muscle twitches (e.g., mentalis muscle) are frequently observed in infants but these decrease with development (Kohyama et al., 1994). In our ongoing study with the analysis of the EMG activity, repetitive masseter twitches contain the components more or less the same as those during chewing behavior in guinea pigs (unpublished observation). In a recent study in rats and mice, a lesion of the trigeminal premotoneurons located laterodorsal to motoneurons (e.g., parvocellular reticular nucleus) significantly decreased the occurrence of the masseter twitch during REM sleep (Anaclet et al., 2010). The trigeminal premotoneurons responsible for RJMs can, at least in part, contribute to the genesis of masseter twitches during REM sleep.

Oromotor activities in sleep

Inhomogeneous nature of the masseter EMG activity can be related to the modalities of oromotor activity that is accompanied by the masseter EMG activities. Oromotor activities such as sleep talking, sighing, grimacing and coughing, can be identified by the polysomnographic recording in humans (Kato et al., 2001b). Some oromotor activities exhibit more specific patterns.

Swallowing

Swallowing is a common oromotor activity during sleep. It occurs at the frequency of 6-10 times per hour of sleep. Swallowing events have been observed more frequently during light NREM sleep and, occasionally, during REM sleep. The occurrence of swallowing is associated with transient arousal activity during sleep, and is probably under the visceral sensory influence (Anderson et al., 1995, Orr et al., 1984). Since swallowing during sleep preserves the coordinated motor patterns such as swallowing apnea and laryngeal movements (Miyawaki et al., 2003), brainstem premotor circuits coordinating swallowing are activated. The role of swallowing during sleep may be to lubricate the esophagus and to contribute to preventing pulmonary aspiration (Kato et al., 2001b).

Rhythmic masticatory muscle activity

RMMA is similar to chewing during wakefulness but the frequency of the masseter EMG bursts is approximately 1 Hz (Lavigne et al., 2001). Approximately 60% of people can show RMMA episodes at a frequency of about 2 times per hour of sleep without tooth grinding (Lavigne et al., 2001). As discussed later, the exaggerated occurrence of RMMA is characteristic of patients with SB. More than half of RMMA concomitantly occur with swallowing (Miyawaki et al., 2003). Whether or not the physiological roles of RMMA during sleep are related to the lubrication of upper alimentary tract and the increase of airway patency, remains to be determined (Lavigne et al., 2003).

Oromandibular myoclonus

Oromandibular myoclonus (OMM) has been reported in subjects with or without SB (Kato et al., 1999; Loi et al., 2007). It is characterized by shock-like jaw movements with sudden, short-duration muscle bursts. Most OMM occurs during light sleep (stages 1 and 2). Concurrent contractions most likely occur in facial muscles. Half of the total myoclonic episodes include repetitive masseter contractions (Kato et al., 1999). The large majority of myoclonic episodes can be easily distinguished from RMMA episodes frequently seen in the patients with SB, since the rhythm of the jaw muscle activations differ between the two (see next section).

Sleep bruxism

SB is characterized by frequent occurrence of the motor episodes with rhythmic activities of the JC muscles (e.g., RMMA) in association with tooth grinding during sleep (Kato and Lavigne, 2010, Lavigne et al., 2003). It is a common sleep-related movement disorder reported by approximately 5-10% of adult population with an age-related decrease from children (15-20%) to the elderly (3%) (Lavigne et al., 2003; Kato and Lavigne, 2010).

Sleep states and micro-arousals

Sleep bruxism is associated with JC muscle activity that contains phasic and tonic bursts (Lavigne et al., 2001; Lavigne et al., 2003). Approximately 90% of SB episodes are characterized by RMMA

that contains rhythmic patterns of phasic bursts (Lavigne et al., 2001; Lavigne et al., 2003) (Fig. 3). The duration of a single SB episode ranges from 5 to 15 s (Lavigne et al., 2001). In otherwise healthy patients with SB, RMMA occurs approximately 3 times more frequently (approximately 6 episodes/h) compared to normal subjects (up to 2 episodes/h). Majority of SB episodes (60-80%) occur during NREM sleep stages 1 and 2, and much fewer during NREM sleep stages 3 and 4 and during REM sleep (Lavigne et al., 2003). SB occurs in clusters during the period when the sleep stage shifts from deep NREM to REM sleep (Huynh et al., 2006a), a period characterized by increased arousal activity such as micro-arousals and cyclic alternating patterns (Macaluso et al., 1998; Kato et al., 2001a). The genesis of RMMA is associated with a physiological sequence of micro-arousal: the masseter contractions of RMMA is preceded by sympathetic activation (4 min), cortical EEG activation (4 s), increase in instantaneous heart rate (approximately 1 s), and suprahyoid muscle activation (0.8 s) (Kato et al., 2001a; Lavigne et al., 2001) (Fig. 3).

Burst characteristics

There are only a few studies in which the masseter EMG patterns of RMMA were compared between SB patients (SBp) and normal subjects (Ns) (Kato et al., 1999; Lavigne et al., 2001). Although the episode duration does not differ between the two groups, the episodes include higher number of master EMG bursts in SBp than in Ns. Burst duration is significantly shorter in SBp (median value: 0.47 to 0.7 s) than in Ns (1.26 s) (Fig. 4A). Masseter burst frequency (e.g., rhythm) tends to be higher in SBp (0.9 Hz) than in Ns (0.7 Hz) (Fig. 4B). When comparing these parameters to those during chewing (Slagter et al., 1993; Blanksma and van Eijden, 1995; Kobayashi et al., 2001; Peyron et al., 2002; Kohyama et al., 2003), burst duration (approximately 0.3 s) is shorter while burst frequency (1.4 Hz) is higher for the RMMA in both populations

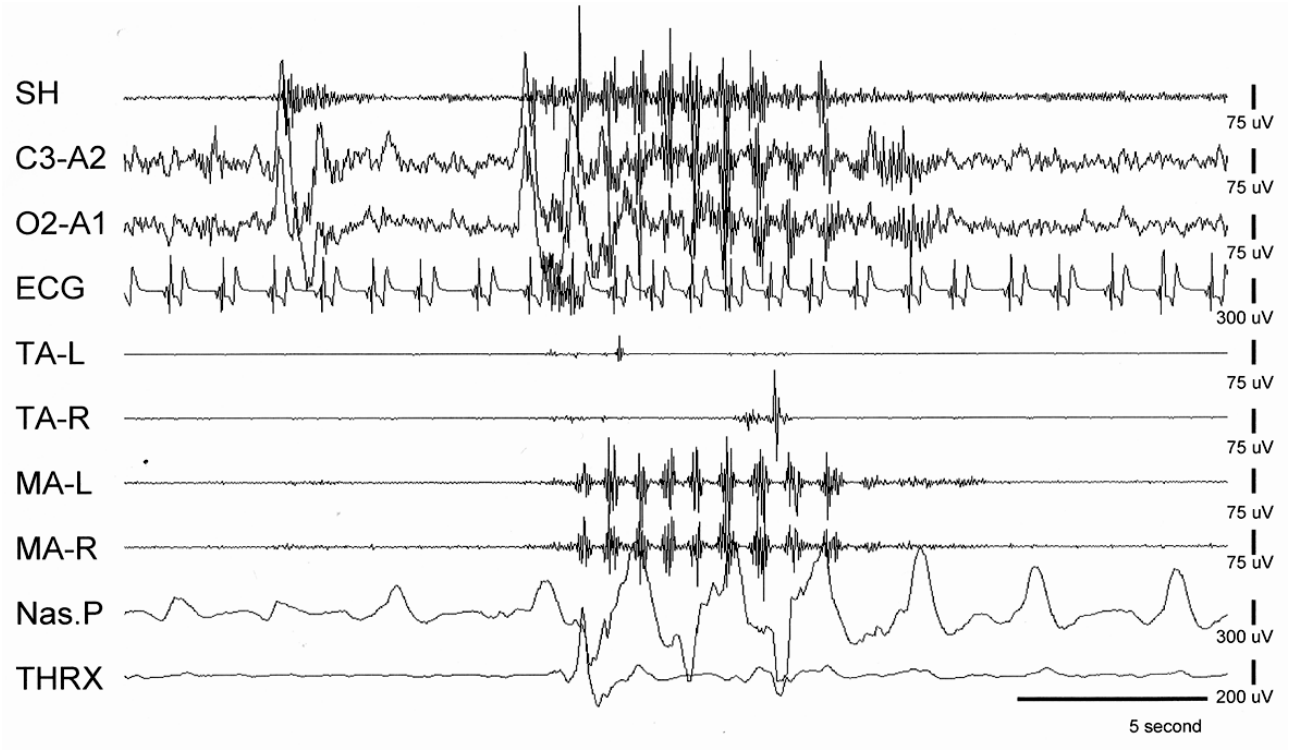

Fig. 3. - Polysomnographic example of a sleep bruxism episode. Rhythmic masseter (MA) bursts occurred in left (L) and right (R) MA muscles. The co-contractions of MA and suprahyoid (SH) muscles were observed. This episode is associated with tachycardia on the electrocardiogram (ECG) and contractions of the anterior tibialis (TA) muscles. An augmentation of respiration is observed in airway pressure (Nas.P) measured with a nasal cannula. During these episodes, EEG changes (C3A2 and O2A1) are obscured by muscle burst artifacts. (From Kato and Lavigne, 2010.)

(Fig. 4AB). On the other hand, repetitive masseter EMG bursts in OMM exhibit shorter burst duration (median: 0.17 s) with the median burst frequency being 1.4 Hz (Kato et al., 1999, Lavigne et al., 2001) (Fig. 4AB). The parameters of the masseter bursts for RMMA or OMM seem more variable than those for chewing. These suggest that the three types of rhythmic masseter EMG activity are not generated by the same neural networks, and that the rhythmic pattern formation or burst generation can be more robust during chewing than during RMMA and OMM. Interestingly, in SBp, mean activity of masseter EMG burst in RMMA is 30-40% higher than in Ns (Lavigne et al., 2001). The relationships between burst frequency, duration and activity differ between RMMA in SBp and Ns, and chewing; during chewing, burst duration is prolonged and bust frequency becomes lower as the activity of masseter EMG bursts increases when harder food is chewed (Hidaka et al., 1997; Peyron et al., 2002; Kohyama et al., 2003) (Fig. 2). It remains to be investigated whether or not the higher masseter EMG activity of the RMMA in SBp reflects the enhanced central drives rather than peripheral influences. Regarding the coordination between the JC and JO muscles, the burst patterns of the masseter and suprahyoid seem to differ between RMMA and chewing. Chewing is characterized by the alternating activations of the JC and JO muscles (Figs. 1 and 2) while RMMA is characterized, according to the result of frequent observations, by rhythmic co-contractions of the JC and JO muscles (Lavigne et al., 2003; Kato and Lavigne, 2010) (Fig. 3). The coordinated patterns of JC and JO muscles during RMMA in relation to jaw movement kinesiology are currently being investigated in our research group.

Motor excitability of SB

When micro-arousals are experimentally induced by sensory stimulation, RMMA is triggered by arousal

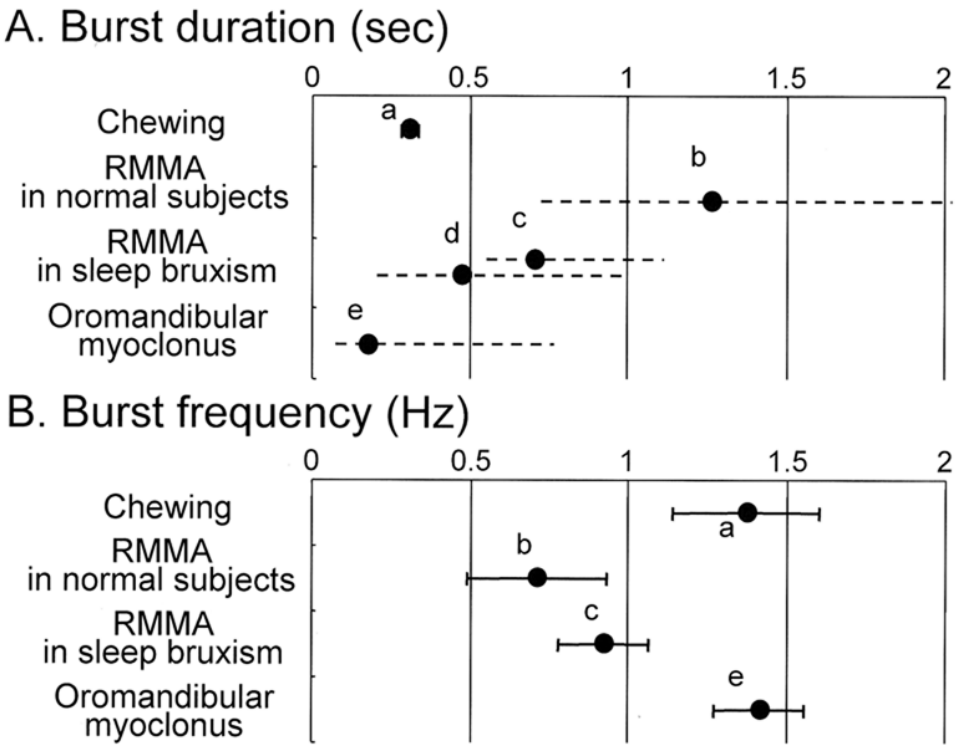

Fig. 4. - Comparisons of the burst duration (A) and frequency (B) between rhythmic jaw movements in chewing and sleep. Circles with dotted error bars indicate the median and range (minimum and maximum). Circles with solid error bars indicate mean ± one standard deviation (SD). a: data from the studies of Blanksma and van Eijden 1995; Kobayashi et al. 2001; Kohyama et al. 2003; Peyron et al. 2002; and Slagter et al. 1993. b and c: from Lavigne et al., 2001. d and e: from Kato et al., 1999.

response seven times more frequently in SBp than Ns, and 86% of induced RMMAs are associated with teeth grinding (Kato et al., 2003). Cortical and cardiac responsiveness to arousing stimuli (auditory, vibrotactile) did not differ between SBp than Ns. In addition, SBp have a normal tonic motor excitability (muscle tone) in the masseter and suprahyoid muscles during sleep. When RMMA is not triggered, muscle tone increases in response to induced arousals are of normal amplitude (Kato et al., 2003). This suggests that SBp may have an increased responsiveness of neural circuits responsible for the genesis of rhythmic jaw motor excitation in response to micro-arousals (Kato et al., 2003).

Increased responsiveness to RMMA in SBp has been reported to decrease after oral administration of clonidine (alpha-2 adrenergic receptor agonist) (Huynh et al., 2006b). It is known that clonidine can acts on REM sleep generator, sympathetic nervous system and trigeminal premotoneurons (Monti, 1987; Katakura and Chandler, 1990). The results of the study showed paradoxical effects of clonidine on the occurrence of RMMA and arousal activity: the former was decreased by 60% while the latter was increased (Carra et al., 2010). Nonetheless, the occurrence of RMMA is associated with arousal activity. The results are further supported by a recent analysis that suggests that transient arousal activity plays a role in providing a permissive condition for the genesis of RMMA, showing that an experimental increase of arousal activity failed to enhance the occurrence of RMMA in Ns and SBp (Carra et al., 2011).

Final summary

Although the information on the masseter EMG activity during sleep is limited, a variety of the masseter EMG phenotypes and jaw movements can be found during sleep. Thus, sleep regulatory systems do not simply bring down the entire neural network of trigeminal motoneurons, excitatory and inhibitory interneurons, sensory afferents, and descending influences from higher centers that orderly regulate masseter EMG activity and jaw movements during wakefulness. However, a combination of the quantitative, spatial and temporal neural circuits eventually sending net facilitatory inputs to trigeminal motoneurons can determine the masseter EMG phenotypes during sleep. Exaggeration of masseter EMG activity during sleep cannot be viewed as a product of a single neural process; it may be caused in association with the general increase of faclitatory influences on motoneurons or an additional activation of specific neural circuits (e.g., sleep bruxism). Further studies are needed to clarify the roles of neural substrates in the genesis and modulation of the distinct patterns of masseter EMG activity during sleep in humans and animals.

Acknowledgement

This work is supported by the Grant-in-Aids (21791888) from the Japan Society for the Promotion of Science.

References

Anaclet C., Pedersen N.P., Fuller P.M., Lu J. Brainstem circuitry regulating phasic activation of trigeminal motoneurons during REM sleep. *PLoS One*, **5**: e8788, 2010.

Anderson C.A., Dick T.E., Orem J. Swallowing in sleep and wakefulness in adult cats. *Sleep*, **18**: 325-329, 1995.

Aston-Jones G., Chiang C., Alexinsky T. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Prog. Brain Res.*, **88**: 501-520, 1991.

Blanksma N.G., van Eijden T.M. Electromyographic heterogeneity in the human temporalis and masseter muscles during static biting, open/close excursions, and chewing. *J. Dent. Res.*, **74**: 1318-1327, 1995.

Brooks P.L. and Peever J.H. Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *J. Neurosci.*, **28**: 3535-3545, 2008.

Burgess C., Lai D., Siegel J., Peever J. An endogenous glutamatergic drive onto somatic motoneurons contributes to the stereotypical pattern of muscle tone across the sleep-wake cycle. *J. Neurosci.*, **28**: 4649-4660, 2008.

Cairns B.E., Fragoso M.C., Soja P.J. Activity of rostral trigeminal sensory neurons in the cat during wakefulness and sleep. *J. Neurophysiol.*, **73**: 2486-2498, 1995.

Cairns B.E., Fragoso M.C., Soja P.J. Active-sleep-related suppression of feline trigeminal sensory neurons: evidence implicating presynaptic inhibition via a process of primary afferent depolarization. *J. Neurophysiol.*, **75**: 1152-1162, 1996.

Carra M.C., Macaluso G.M., Rompre P.H., Huynh N., Parrino L., Terzano M.G., Lavigne G.J. Clonidine has a paradoxical effect on cyclic arousal and sleep bruxism during NREM sleep. *Sleep*, **33**: 1711-1716, 2010.

Carra M.C., Rompré P.H., Kato T., Parrino L., Terzano M.G., Lavigne G.J., Macaluso G.M. Sleep bruxism and sleep arousal: an experimental challenge to assess the role of cyclic alternating pattern. *J. Oral Rehabil.*, **38**: 635-642, 2011.

Chandler S.H., Chase M.H., Nakamura Y. Intracellular analysis of synaptic mechanisms controlling trigeminal motoneuron activity during sleep and wakefulness. *J. Neurophysiol.*, **44**: 359-371, 1980.

Chase M.H. Brain stem somatic reflex activity in neonatal kittens during sleep and wakefulness. *Physiol. Behav.*, **7**: 165-172, 1971.

Chase M.H. Confirmation of the consensus that glycinergic postsynaptic inhibition is responsible for the atonia of REM sleep. *Sleep*, **31**: 1487-1491, 2008.

Clarke N.G. and Townsend G.C. Distribution of nocturnal bruxing patterns in man. *J. Oral Rehabil.*, **11**: 529-534, 1984.

Evarts E.V. Temporal Patterns of Discharge of Pyramidal Tract Neurons during Sleep and Waking in the Monkey. *J. Neurophysiol.*, **27**: 152-171, 1964.

Fenik V.B., Davies R.O., Kubin L. REM sleep-like atonia of hypoglossal (XII) motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am. J. Respir. Crit. Care Med.*, **172**: 1322-1330, 2005.

Foo H. and Mason P. Movement-related discharge of ventromedial medullary neurons. *J. Neurophysiol.*, **93**: 873-883, 2005.

Fort P., Luppi P.H., Sakai K., Salvert D., Jouvet M. Nuclei of origin of monoaminergic, peptidergic, and cholinergic afferents to the cat trigeminal motor nucleus: a double-labeling study with cholera-toxin as a retrograde tracer. *J. Comp. Neurol.*, **301**: 262-275, 1990.

Funk G.D. Are all motoneurons created equal in the eyes of REM sleep and the mechanisms of muscle atonia? *Sleep*, **31**: 1479-1482, 2008.

Gallo L.M., Gross S.S., Palla S. Nocturnal masseter EMG activity of healthy subjects in a natural environment. *J. Dent. Res.*, **78**: 1436-1444, 1999.

Halasz P., Terzano M., Parrino L., Bodizs R. The nature of arousal in sleep. *J. Sleep Res.*, **13**: 1-23, 2004.

Hashimoto N., Katayama T., Ishiwata Y., Nakamura Y. Induction of rhythmic jaw movements by stimulation of the mesencephalic reticular formation in the guinea pig. *J. Neurosci.*, **9**: 2887-2901, 1989.

Hidaka O., Morimoto T., Masuda Y., Kato T., Matsuo R., Inoue T., Kobayashi M., Takada K. Regulation of masticatory force during cortically induced rhythmic jaw movements in the anesthetized rabbit. *J. Neurophysiol.*, **77**: 3168-3179, 1997.

Hollowell D.E. and Suratt P.M. Mandible position and activation of submental and masseter muscles during sleep. *J. Appl. Physiol.*, **71**: 2267-2273, 1991.

Horner R.L., Sanford L.D., Pack A.I., Morrison A.R. Activation of a distinct arousal state immediately after spontaneous awakening from sleep. *Brain Res.*, **778**: 127-134, 1997.

Huynh N., Kato T., Rompre P.H., Okura K., Saber M., Lanfranchi P.A., Montplaisir J.Y., Lavigne G.J. Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity. *J. Sleep Res.*, **15**: 339-346, 2006a.

Huynh N., Lavigne G.J., Lanfranchi P.A., Montplaisir J.Y., de Champlain J. The effect of 2 sympatholytic medications – propranolol and clonidine – on sleep bruxism: experimental randomized controlled studies. *Sleep*, **29**: 307-316, 2006b.

Iida C., Oka A., Moritani M., Kato T., Haque T., Sato F., Nakamura M., Uchino K., Seki S., Bae Y.C., Takada K., Yoshida A. Corticofugal direct projections to primary afferent neurons in the trigeminal mesencephalic nucleus of rats. *Neuroscience*, **169**: 1739-1757, 2010.

Ikeda T., Nishigawa K., Kondo K., Takeuchi H., Clark G.T. Criteria for the detection of sleep-associated bruxism in humans. *J. Orofac. Pain.*, **10**: 270-282, 1996.

Inoue M., Yamamura K., Nakajima T., Yamada Y. Changes in reflex responses of the masseter and digastric muscles during sleep in freely behaving rabbits. *Neurosci. Res.*, **34**: 37-44, 1999.

Jacobs B.L., Martin-Cora F.J., Fornal C.A. Activity of medullary serotonergic neurons in freely moving animals. *Brain Res. Brain Res. Rev.*, **40**: 45-52, 2002.

Jacobson A., Kales A., Lehmann D., Hoedemaker F.S. Muscle Tonus in Human Subjects during Sleep and Dreaming. *Exp. Neurol.*, **10**: 418-424, 1964.

Katakura N. and Chandler S.H. An iontophoretic analysis of the pharmacologic mechanisms responsible for trigeminal motoneuronal discharge during masticatory-like activity in the guinea pig. *J. Neurophysiol.*, **63**: 356-369, 1990.

Kato T., Montplaisir J.Y., Blanchet P.J., Lund J.P., Lavigne G.J. Idiopathic myoclonus in the oromandibular region during sleep: a possible source of confusion in sleep bruxism diagnosis. *Mov. Disord.*, **14**: 865-871, 1999.

Kato T., Rompre P., Montplaisir J.Y., Sessle B.J., Lavigne G.J. Sleep bruxism: an oromotor activity secondary to micro-arousal. *J. Dent Res.*, **80**: 1940-1944, 2001a.

Kato T., Thie N.M., Montplaisir J.Y., Lavigne G.J. Bruxism and orofacial movements during sleep. *Dent. Clin. North Am.*, **45**: 657-684, 2001b.

Kato T., Montplaisir J.Y., Guitard F., Sessle B.J., Lund J.P., Lavigne G.J. Evidence that experimentally induced sleep bruxism is a consequence of transient arousal. *J. Dent. Res.*, **82**: 284-288, 2003.

Kato T., Montplaisir J.Y., Lavigne G.J. Experimentally induced arousals during sleep: a cross-modality matching paradigm. *J. Sleep Res.*, **13**: 229-238, 2004.

Kato T., Akiyama S., Kato Y., Yamashita S., Masuda Y., Morimoto T. The occurrence of spontaneous functional and nonfunctional orofacial activities in subjects without pain under laboratory conditions: a descriptive study. *J. Orofac. Pain.*, **20**: 317-324, 2006.

Kato T., Masuda Y., Kanayama H., Morimoto T. Muscle activities are differently modulated between masseter and neck muscle during sleep-wake cycles in guinea pigs. *Neurosci Res.*, **58**: 265-271, 2007a.

Kato T., Masuda Y., Morimoto T. Patterns of masseter muscle activities during sleep in guinea pigs. *Arch. Oral. Biol.*, **52**: 385-386, 2007b.

Kato T. and Lavigne G.J. Sleep bruxism: a sleep related movement disorder. *Sleep Med. Clin.*, **5**: 9-35, 2010.

Kato T., Masuda Y., Kanayama H., Nakamura N., Yoshida A., Morimoto T. Heterogeneous activity level of jaw-closing and -opening muscles and its association with arousal levels during sleep in the guinea pig. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **298**: R34-42, 2010.

Kawamura Y. and Tsukamoto S. Analysis of jaw movements from the cortical jaw motor area and amygdala. *Jpn. J. Physiol.*, **10**: 471-488, 1960.

Kobayashi T., Honma K., Shingaki S., Nakajima T. Changes in masticatory function after orthognathic treatment in patients with mandibular prognathism. *Br. J. Oral Maxillofac. Surg.*, **39**: 260-265, 2001.

Kohyama J., Shimohira M., Iwakawa Y. Brainstem control of phasic muscle activity during REM sleep: a review and hypothesis. *Brain Dev.*, **16**: 81-91, 1994.

Kohyama K., Mioche L., Bourdiol P. Influence of age and dental status on chewing behaviour studied by EMG recordings during consumption of various food samples. *Gerodontology*, **20**: 15-23, 2003.

Kolta A., Westberg K.G., Lund J.P. Identification of brainstem interneurons projecting to the trigeminal motor nucleus and adjacent structures in the rabbit. *J. Chem. Neuroanat.*, **19**: 175-195, 2000.

Kubin L. Adventures and tribulations in the search for the mechanisms of the atonia of REM sleep. *Sleep*, **31**: 1473-1476, 2008.

Lavigne G., Kim J.S., Valiquette C., Lund J.P. Evidence that periodontal pressoreceptors provide positive feedback to jaw closing muscles during mastication. *J. Neurophysiol.*, **58**: 342-358, 1987.

Lavigne G.J., Rompre P.H., Poirier G., Huard H., Kato T., Montplaisir J.Y. Rhythmic masticatory muscle activity during sleep in humans. *J. Dent. Res.*, **80**: 443-448, 2001.

Lavigne G.J., Kato T., Kolta A., Sessle B.J. Neurobiological mechanisms involved in sleep bruxism. *Crit. Rev. Oral. Biol. Med.*, **14**: 30-46, 2003.

Lavigne G., Brousseau M., Kato T., Mayer P., Manzini C., Guitard F., Monplaisir J. Experimental pain perception remains equally active over all sleep stages. *Pain*, **110**: 646-655, 2004.

Leung C.G. and Mason P. Physiological properties of raphe magnus neurons during sleep and waking. *J. Neurophysiol.*, **81**: 584-595, 1999.

Liu Z.J., Masuda Y., Inoue T., Fuchihata H., Sumida A., Takada K., Morimoto T. Coordination of cortically induced rhythmic jaw and tongue movements in the rabbit. *J. Neurophysiol.*, **69**: 569-584, 1993.

Loi D., Provini F., Vetrugno R., D'Angelo R., Zaniboni A., Montagna P. Sleep-related faciomandibular myoclonus: A sleep-related movement disorder different from bruxism. *Mov. Disord.*, **22**: 1819-1822, 2007.

Lu J.W., Mann G.L., Ross R.J., Morrison A.R., Kubin L. Differential effect of sleep-wake states on lingual and dorsal neck muscle activity in rats. *Respir. Physiol. Neurobiol.*, **147**: 191-203, 2005.

Lund J.P. Mastication and its control by the brain stem. *Crit. Rev. Oral. Biol. Med.*, **2**: 33-64, 1991.

Lund J.P., Kolta A., Westberg K.G., Scott G. Brainstem mechanisms underlying feeding behaviors. *Curr. Opin. Neurobiol.*, **8**: 718-724, 1998.

Macaluso G.M., Guerra P., Di Giovanni G., Boselli M., Parrino L., Terzano M.G. Sleep bruxism is a disorder related to periodic arousals during sleep. *J. Dent. Res.*, **77**: 565-573, 1998.

Marchiafava P.L. and Pompeiano O. Pyramidal Influences of Spinal Cord during Desynchronized Sleep. *Arch. Ital. Biol.*, **102**: 500-529, 1964.

Mascaro M.B., Prosdocimi F.C., Bittencourt J.C., Elias C.F. Forebrain projections to brainstem nuclei involved in the control of mandibular movements in rats. *Eur. J. Oral Sci.*, **117**: 676-684, 2009.

Masuda Y., Morimoto T., Hidaka O., Kato T., Matsuo R., Inoue T., Kobayashi M., Taylor A. Modulation of jaw muscle spindle discharge during mastication in the rabbit. *J. Neurophysiol.*, **77**: 2227-2231, 1997.

Miyamoto K., Yamada K., Ishizuka Y., Morimoto N., Tanne K. Masseter muscle activity during the whole day in young adults. *Am. J. Orthod. Dentofacial Orthop.*, **110**: 394-398, 1996.

Miyawaki S., Lavigne G.J., Pierre M., Guitard F., Montplaisir J.Y., Kato T. Association between sleep bruxism, swallowing-related laryngeal movement, and sleep positions. *Sleep*, **26**: 461-465, 2003.

Monti J.M. Disturbances of sleep and wakefulness associated with the use of antihypertensive agents. *Life Sci.*, **41**: 1979-1988, 1987.

Morales F.R. and Chase M.H. Intracellular recording of lumbar motoneuron membrane potential during sleep and wakefulness. *Exp. Neurol.*, **62**: 821-827, 1978.

Murray G.M., Phanachet I., Uchida S., Whittle T. The role of the human lateral pterygoid muscle in the control of horizontal jaw movements. *J. Orofac. Pain*, **15**: 279-292; discussion 292-305, 2001.

Nagase Y., Moritani M., Nakagawa S., Yoshida A., Takemura M., Zhang L.F., Kida H., Shigenaga Y. Serotonergic axonal contacts on identified cat trigeminal motoneurons and their correlation with medullary raphe nucleus stimulation. *J. Comp. Neurol.*, **384**: 443-455, 1997.

Nakamura Y., Goldberg L.J., Chandler S.H., Chase M.H. Intracellular analysis of trigeminal motoneuron activity during sleep in the cat. *Science*, **199**: 204-207, 1978.

Nakamura Y. and Katakura N. Generation of masticatory rhythm in the brainstem. *Neurosci. Res.*, **23**: 1-19, 1995.

Okura K., Kato T., Montplaisir J.Y., Sessle B.J., Lavigne G.J. Quantitative analysis of surface EMG activity of cranial and leg muscles across sleep stages in human. *Clin. Neurophysiol.*, **117**: 269-278, 2006.

Orr W.C., Johnson L.F., Robinson M.G. Effect of sleep on swallowing, esophageal peristalsis, and acid clearance. *Gastroenterology*, **86**: 814-819, 1984.

Pedroarena C., Castillo P., Chase M.H., Morales F.R. The control of jaw-opener motoneurons during active sleep. *Brain Res.*, **653**: 31-38, 1994.

Peyron M.A., Lassauzay C., Woda A. Effects of increased hardness on jaw movement and muscle activity during chewing of visco-elastic model foods. *Exp. Brain Res.*, **142**: 41-51, 2002.

Powell R.N. and Zander H.A. The Frequency and Distribution of Tooth Contact during Sleep. *J. Dent. Res.*, **44**: 713-717, 1965.

Quattrochi J.J., Shapiro J., Verrier R.L., Hobson J.A. Transient cardiorespiratory events during NREM sleep: a feline model for human microarousals. *J. Sleep Res.*, **9**: 185-191, 2000.

Rampon C., Peyron C., Petit J.M., Fort P., Gervasoni D., Luppi P.H. Origin of the glycinergic innervation of the rat trigeminal motor nucleus. *Neuroreport*, **7**: 3081-3085, 1996.

Sakai K. and Crochet S. Differentiation of presumed serotonergic dorsal raphe neurons in relation to behavior and wake-sleep states. *Neuroscience*, **104**: 1141-1155, 2001.

Shigenaga Y., Bae Y.C., Moritani M., Yoshida A. Spatial distribution patterns of excitatory and inhibitory synapses in the dendritic tree differ between jaw-closing and -opening motoneurons. *Arch. Oral. Biol.*, **52**: 321-324, 2007.

Slagter A.P., Bosman F., van der Glas H.W., van der Bilt A. Human jaw-elevator muscle activity and food comminution in the dentate and edentulous state. *Arch. Oral. Biol.*, **38**: 195-205, 1993.

Soja P.J. Glycine-mediated postsynaptic inhibition is responsible for REM sleep atonia. *Sleep*, **31**: 1483-1486, 2008.

Takahashi K., Kayama Y., Lin J.S., Sakai K. Locus coeruleus neuronal activity during the sleep-waking cycle in mice. *Neuroscience*, **169**: 1115-1126, 2010.

Turman J., Jr. and Chandler S.H. Immunohistochemical evidence for GABA and glycine-containing

trigeminal premotoneurons in the guinea pig. *Synapse*, **18**: 7-20, 1994a.

Turman J.E., Jr. and Chandler S.H. Immunohistochemical localization of glutamate and glutaminase in guinea pig trigeminal premotoneurons. *Brain Res.*, **634**: 49-61, 1994b.

Van Der Bilt A. Assessment of mastication with implications for oral rehabilitation: a review. *J. Oral Rehabil.*, **38**: 754-780, 2011.

Woda A., Pionchon P., Palla S. Regulation of mandibular postures: mechanisms and clinical implications. *Crit. Rev. Oral. Biol. Med.*, **12**: 166-178, 2001.

Yoshida A., Taki I., Chang Z., Iida C., Haque T., Tomita A., Seki S., Yamamoto S., Masuda Y., Moritani M., Shigenaga Y. Corticofugal projections to trigeminal motoneurons innervating antagonistic jaw muscles in rats as demonstrated by anterograde and retrograde tract tracing. *J. Comp. Neurol.*, **514**: 368-386, 2009.