NEUROBIOLOGICAL MECHANISMS INVOLVED IN SLEEP BRUXISM

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ABSTRACT: Sleep bruxism (SB) is reported by 8% of the adult population and is mainly associated with rhythmic masticatory muscle activity (RMMA) characterized by repetitive jaw muscle contractions (3 bursts or more at a frequency of 1 Hz). The consequences of SB may include tooth destruction, jaw pain, headaches, or the limitation of mandibular movement, as well as tooth-grinding sounds that disrupt the sleep of bed partners. SB is probably an extreme manifestation of a masticatory muscle activity occurring during the sleep of most normal subjects, since RMMA is observed in 60% of normal sleepers in the absence of grinding sounds. The pathophysiology of SB is becoming clearer, and there is an abundance of evidence outlining the neurophysiology and neurochemistry of rhythmic jaw movements (RJM) in relation to chewing, swallowing, and breathing. The sleep literature provides much evidence describing the mechanisms involved in the reduction of muscle tone, from sleep onset to the atonia that characterizes rapid eye movement (REM) sleep. Several brainstem structures (*e.g.*, reticular pontis oralis, pontis caudalis, parvocellularis) and neurochemicals (*e.g.*, serotonin, dopamine, gamma aminobutyric acid [GABA], noradrenaline) are involved in both the genesis of RJM and the modulation of muscle tone during sleep. It remains unknown why a high percentage of normal subjects present RMMA during sleep and why this activity is three times more frequent and higher in amplitude in SB patients. It is also unclear why RMMA during sleep is characterized by co-activation of both jaw-opening and jaw-closing muscles instead of the alternating jaw-opening and jaw-closing muscle activity pattern typical of chewing. The final section of this review proposes that RMMA during sleep has a role in lubricating the upper alimentary tract and increasing airway patency. The review concludes with an outline of questions for future research.

Key words. Sleep bruxism (SB), mastication, chewing, rhythmic jaw movements (RJM), rhythmic masticatory muscle activity (RMMA), central pattern generator (CPG).

(I) Introduction

The neurobiology of sleep bruxism (SB) is poorly understood in terms of etiology and pathophysiology. This review discusses the interaction between mechanisms involved in the genesis of rhythmic oro-mandibular movements and their interactions in sleep physiology. Special attention is given to the role of the cardiac/autonomic system, as well as to brain cortical electroencephalographic (EEG) activation and the neurochemical processes associated with motoneuron excitability in relation to sleep. The role of peripheral sensory inputs (*e.g.*, periodontal) and of cognitive-behavioral factors (*e.g.*, stress, anxiety, personality) in SB has been covered elsewhere, and we refer readers to recent publications (Clark *et al*., 1999; Major *et al*., 1999; Bader and Lavigne, 2000; Kato *et al*., 2003a).

Bruxism is an involuntary activity of the jaw musculature that is characterized, in awake individuals, by jaw clenching (so-called awake bruxism) and, on rare occasions, by tooth gnashing and/or grinding. During SB, both clenching and tooth-grinding are observed. SB can cause tooth destruction, temporomandibular dysfunction (*e.g.*, jaw pain or movement limitation), occasional headaches, and the disruption of the bed partner's sleep due to the grinding sounds (Bader and Lavigne, 2000; Lavigne and Manzini, 2000). When bruxism occurs in the presence of a neurological or psychiatric disorder (*e.g.*, Parkinsonism, depression, schizophrenia), or following the use of medication, it is termed 'secondary' (Lavigne and Manzini, 2000). The prevalence of awake bruxism in the general population is approximately 20%, while the prevalence of SB is about 8% (Reding *et al*., 1966; Glaros, 1981; Lavigne and Montplaisir, 1994; Ohayon *et al*., 2001). Complaints of tooth-grinding occurring during sleep decline over time, from 14% in children to 8% in adults to 3% in patients over 60 years of age (Lavigne and Montplaisir, 1994; Laberge *et al*., 2000). Awake bruxism can occur alone or concomitantly with SB. Some patients complain of jaw tightness and grinding sounds daily or nightly, whereas others report these infrequently (Rugh and Harlan, 1988; Lavigne and Manzini, 2000). In cases of severe and frequent SB, the variation of the number of oro-motor episodes *per* hour of sleep is 25%, and the variation of tooth-grinding frequency is higher, at 53.5% (Lavigne *et al*., 2001b).

IDENTIFICATION OF SB

In patients with SB, awareness or reports of current tooth-grinding are essential elements for the diagnosis of this condition. The appearance of tooth wear and the patient's reports of jaw muscle tightness, discomfort, and pain are less reliable (Bader and Lavigne, 2000; Lavigne and Manzini, 2000). For research purposes, SB and tooth-grinding are frequently monitored with polygraphic and audiovisual recording systems in a laboratory milieu (*i.e.*, polysomnography) (Reding *et al*., 1968; Lavigne *et al*., 1996). An alternative is the use of a portable system at home, in the natural sleep environment (Rugh and Harlan, 1988; Ikeda *et al*., 1996; Gallo *et al*., 1997). Although this is less expensive than the laboratory recordings, full polysomnography allows for the recognition of most SB motor activity that can otherwise be confounded by ongoing jaw activity, such as swallowing, coughing, sleep-talking, sighing, or myoclonus (Velly-Miguel *et al*., 1992; Lavigne *et al*., 1996; Kato *et al*., 1999, 2001b; Lavigne and Manzini, 2000).

TABLE 1

Pathophysiology of Sleep Bruxism (Kato *et al.*, 2001b; Lavigne and Manzini, 2000)

Exogenous/Peripheral Factors	Endogenous
• Stress-anxiety • Environmental influences (*e.g.*, familial, jaw-clenching reactions, tongue habits) • Occlusal interferences (controversy) • Medication (*e.g.*, L-dopa, neuroleptics, amphetamine, SSRI*) • Substance abuse (*e.g.*, cocaine, alcohol)	• Personality (*e.g.*, anxious) • Genetic (no proven transmission) • Neurochemicals (*e.g.*, dopamine, noradrenaline, serotonin); see text. • Neurological disorders (*e.g.*, Parkinson, Meige syndrome/oral tardive dyskinesia, RBD, olivopontocerebellar atrophy, cerebellar hemorrhage) • Psychiatric-related disorders (*e.g.*, dementia, mental retardation, tics/Tourette's syndrome) • Sleep disorders (*e.g.*, PLMS, apnea, RBD)

* SSRI, selective serotonin re-uptake inhibitors; PLMS, periodic limb movements during sleep; and RBD, REM sleep behavior disorder.

SB is associated with jaw muscle activity defined as one of three types: rhythmic jaw muscle activity, termed 'phasic' (three or more bursts of muscle contractions at a frequency of 1 Hz); sustained activity, termed 'tonic' (a contraction lasting more than 2 sec); or a mixture of both types (Ware and Rugh, 1988; Lavigne *et al*., 1996). Over 88% of SB episodes, based on electromyographic (EMG) recordings, are of either the phasic or mixed type. In SB, jaw muscle activity mainly occurs during light sleep (60-80%) at a mean frequency of 5.4 to 5.8 episodes *per* hour of sleep (Lavigne *et al*., 1996, 2001c; Macaluso *et al*., 1998b; Saber *et al*., 2002).

During sleep, close to 60% of normal subjects also show rhythmic masticatory muscle activity (RMMA), which occurs at a frequency of 1.8 episodes *per* hour of sleep (Gastaut *et al*., 1965; Halász *et al*., 1985; Lavigne *et al*., 2001c). However, the frequency of RMMA is three times lower in normal subjects than in SB patients, the muscle contractions are of a lower amplitude, and no tooth-grinding sound complaint is reported (Lavigne *et al*., 2001c).

Another frequent oro-facial activity that needs to be distinguished from SB is oro-mandibular myoclonus. A myoclonus is characterized by a sudden and brief (< 0.25 sec) jerk of a limb, neck, or jaw muscle. When this occurs at the onset of sleep, it is normal and termed a 'hypnic' jerk (Broughton *et al*., 1985). Oro-mandibular myoclonus is observed across all sleep stages and is characterized by much briefer muscle contractions. It also occurs in 10% of patients with a history of tooth-grinding (Kato *et al*., 1999). A recent report has used the term 'faciomandibular myoclonus' for patients complaining of tongue-biting and bleeding during sleep; the jerks were observed in the masseter muscle (supplied by the Vth cranial nerve) and orbicularis and oris muscles (supplied by the VIIth cranial nerve) (Montagna *et al*., 2001).

Finally, the rare occurrence of several neurological (*e.g.*, movement) or sleep disorders must be considered in the differential diagnosis of SB. SB has been observed with Huntington's disease, tics, hemifacial spasm, Parkinson's disease, neuroleptic-induced tardive dyskinesia, and violent parasomnias such as the REM (rapid eye movement) behavior disorders (RBD) (see Table 1) (Kato *et al*., 2001b).

REM BEHAVIOR DISORDERS (RBD)

RBDs are sleep disorders that are not fully understood. The physiological mechanism responsible for the muscle atonia (nearly complete reduction in muscle tone) that usually characterizes the REM sleep stage (see Section II below) is either reversed or dysfunctional (see Section IV below). The causes of RBD are multiple, ranging from toxic metabolites, vascular or tumoral lesions, and infections, to neuro-degenerative, congenital, or idiopathic factors (Schenck and Mahowald, 1992; Schenck *et al*., 1997; Mahowald and Schenck, 2000). RBD and SB are easily distinguished, since SB rarely occurs in REM, and, unlike the localized movements observable in RMMA or oro-mandibular myoclonus, movements in RBD patients are more organized and generalized to several body parts; for example, RBD patients' dreams can be associated with gestures and body movements such as crawling, jumping, or punching. These movements can also be the cause of bodily injuries (Mahowald and Schenck, 2000).

(II) Sleep Physiology

In human adults, sleep is divided into two major types occurring in 3-6 cycles at an interval of 60-90 minutes: (1) non-REM sleep (so-called 'quiet' sleep) that includes light sleep (stages 1 and 2) and deep sleep (stages 3 and 4 or delta sleep); and (2) REM sleep (so-called 'active' or 'paradoxical' sleep). The first third of the sleep period is characterized by a dominance of deep sleep (delta sleep), while REM sleep dominates the last period toward morning. As humans pass from wakefulness to deep sleep, brain electrical (electroencephalographic, EEG) activity slows, and autonomic cardiac sympathetic activity (*e.g.*, as measured by spectral analysis of heart rate interval in the low-frequency 0.05-0.15 Hz range) diminishes.

During sleep stage 2, EEG traces are also characterized by EEG K-complexes (brief bipolar EEG waves) that occur from

once to five times *per* minute and represent a cortical response to exogenous (*e.g.*, sound) or endogenous (*e.g.*, change in blood pressure) events. These events are clearly associated with periodic limb movement (PLM) during sleep (Montplaisir *et al*., 1996) but not with SB, as described in Section V below (Lavigne *et al*., 2002). The EEG spindles (7-14 Hz,) that result from the firing of thalamo-cortical neurons are another type of oscillation observed in light sleep (stages 1 and 2). The spindles contribute to non-REM EEG synchrony (Amzica and Steriade, 1997), as described below in Section V.

During deep sleep stages 3 and 4, the EEG slow-wave activity and parasympathetic-vagal cardiac activity dominate (*e.g.*, high-frequency 0.15-0.5Hz). In REM sleep, brain EEG activity increases and becomes highly desynchronized or, as recently termed, highly activated (Steriade, 2000). REM sleep is also characterized by a return of variable cardiac sympathetic activity that is sometimes higher than in awake levels (Baharav *et al*., 1995; Nance and Hoy, 1996; Bonnet and Arand, 1997). Moreover, a paradoxical phenomenon is observed during REM sleep: Phasic eye movements occur upon a background of parallel depression in muscle tone to a level where the jaw and limb muscles experience a state of atonia (*e.g.*, nearly complete EMG silence) (Gottesmann, 1997; Carskadon and Dement, 2000; Siegel, 2000; Lavigne *et al*., 2001a).

Awakenings are frequently observed over a normal sleep period. These are characterized by a transient (> 10 sec or 15 sec) sleep stage shift to a lighter state, such as sleep stage 1, with a concomitant rise in muscle tone. Awakenings differ from the state of full wakening wherein the subject, for instance, responds more easily to a question. Micro-arousals can also occur; these are sleep perturbations characterized by a transient increase (for 3 to 10 or 15 sec) in EEG fast-wave activity, with or without an increase in EMG activity and cardiac rhythm (Am Sleep Disord Assoc, 1992; Roehrs *et al*., 2000). When an arousal is scored with a respiratory event (*e.g.*, apnea), it is termed a respiratory arousal, and if it is observed with body movements (*e.g.*, PLM or SB), it is termed a movement arousal. Note that some arousals may occur in the absence of EEG changes. The high frequency of sleep arousal incidents could result in daytime dysfunction (*e.g.*, reduced alertness, increased risk of traffic accident), as has been observed in apneic patients (Bonnet, 2000). The term 'sleep fragmentation' is used when sleep is characterized by an elevated frequency of awakenings, arousals, sleep stage shifts (*e.g.*, from deep to light sleep), and movements in comparison with values estimated in the sleep of similarly aged 'normals'. In young adults, for example, an arousal index below 15 *per* hour of sleep is considered within the normal range (Mathur and Douglas, 1995; Boselli *et al*., 1998). Clusters of transient brain, cardiac, and muscle activations seen in non-REM sleep are termed 'cyclic alternating pattern' (CAP). These are frequently associated with body movements (*e.g.*, PLM, SB) or respiratory events (*e.g.*, sleep apnea) (Terzano and Parrino, 1993). The CAP activations are separated by 20- to 40-second intervals and are followed by long periods of relatively stable EEG, electrocardiographic (ECG), and EMG activity.

(III) Physiology of Rhythmic Movements

Chewing is a repetitive motor activity, which, like locomotion and respiration, is driven by cellular networks within the central nervous system (Lund *et al*., 1984a; Stein *et al*., 1997). These networks are termed the central pattern generator (CPG). They are organized to initiate and maintain the motor activity through pattern generation and rhythm generation. The integration of influences from sensory inputs, such as those from muscle spindles, joint, mucosal, and dental (*e.g.*, periodontal) receptors, is necessary to control or fine-tune rhythmic jaw movements (Nakamura and Katakura, 1995; Lund *et al*., 1998). The CPG concept has replaced Sherrington's original description of repetitive movements resulting from a series of opposing reflexes (*e.g.*, alternation of extensor and flexor muscle reflexes) (Grillner, 1981; Rossignol, 1996). This journal has already published an excellent review highlighting the importance of tongue, oral, pharyngeal, and esophageal muscle synchronization during chewing, swallowing, and respiration (Sawczuk and Mosier, 2001). In the next section, we will review the mechanisms involved in mastication and respiration, since both are of clinical interest in sleep disorders (*e.g.*, bruxism and apnea).

(A) MASTICATION

Masticatory muscle activities are integral components of feeding (*e.g.*, sucking, chewing, swallowing), talking, oral respiration, and airway maintenance, as well as facial expressions (*e.g.*, a lion or dog baring its teeth) and emotional reactions (*e.g.*, anxiety-related jaw clenching). In humans, following the oral insertion of food, the jaw muscle activity associated with repetitive masticatory movements alternates between jaw-opening muscles (*e.g.*, digastric) and jaw-closing muscles (*e.g.*, masseter, temporalis, medial pterygoid). The masticatory CPG (the 'chewing center') is thought to be composed of two groups: the rhythm generator and the burst generator (Lund, 1991; Lund *et al*., 1998). The first generates the basic masticatory rhythm, while the second adapts the rhythm according to sensory inputs from the oral cavity in particular, and generates the spatio-temporal pattern of burst activity in the masticatory motoneurons supplying the muscles, so that the movement becomes appropriate for the food bolus, size, viscosity, and temperature. Several elements of the masticatory CPG also interact with the respiratory CPG and the swallowing CPG (the 'swallowing center') to avoid food aspiration (Sawczuk and Mosier, 2001). Salivary flow is also an important activity in mastication by allowing the food bolus to be softened and by lubricating the oral tissues to facilitate chewing and swallowing (Thie *et al*., 2002).

Genesis and control of mastication

The role of the cerebral cortex and subcortical influences in the genesis of rhythmic oro-facial activity, such as mastication, was demonstrated in animals over a century ago (Ferrier, 1886). This discovery was later reproduced in rabbits (Bremer, 1923) and in other species, including monkeys (Vogt and Vogt, 1926), cats (Magoun *et al*., 1933), and guinea pigs (Goldberg and Tal, 1978). The cortico-bulbar (brainstem) pathway that drives mastication seems to be a unique feature of the oro-facial motor system, since both locomotion and respiration cannot be triggered by electrical micro-stimulation of cortical motor areas. In recent years, mapping of specific cortical masticatory sensorimotor areas has improved our understanding of the neuronal masticatory network (Nakamura *et al*., 1976; Lund *et al*., 1984b; Huang *et al*., 1989a). In primates, RJMs are triggered by microstimulation of the primary face motor cortex (MI), primary face somatosensory cortex (SI), and cortical masticatory areas (CMA) (Lund and Lamarre, 1974; Huang *et al*., 1989a). It should

also be noted that the CMA is not exclusive to the genesis of rhythmic chewing, since micro-stimulation in these other cortical areas in awake monkeys also triggers swallowing, an activity that has also been observed in close to 60% of SB and sleep RMMA episodes in humans (Martin *et al*., 1999; Miyawaki *et al*., 2002 ([accepted]).

Cortically evoked RJMs result in a pattern of jaw-opening and jaw-closing muscle activity that resembles natural chewing. However, in monkeys, in comparison with natural chewing, the duration of the opening-closing cycles following cortical stimulation is twice as long and the EMG burst amplitude half the size (Huang *et al*., 1989b). It is noteworthy that the major differences between natural food mastication or cortically driven masticatory movements and sleep RMMA or SB motor activity are that: (1) mastication is an awake and voluntary-automatic behavior associated with feeding, while RMMA and SB occur spontaneously during sleep; and (2) mastication manifests alternating activity of the jaw-opening and jaw-closing muscles, while in RMMA and SB episodes, the jaw-opening and jaw-closing muscles show a co-contraction (also termed co-activation).

In humans, voluntary chewing is associated with maximal cortical EEG activity, at the central position of the head-skull, which corresponds to the CMA area in monkeys (Yoshida *et al*., 2000). Using brain Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) technologies, investigators have observed that the cortical primary somatosensory area, supplementary motor area, insula, cerebellum, and striatum of basal ganglia were activated during gum chewing (Momose *et al*., 1997; Onozuka *et al*., 2002). Studies using fMRI also reveal activation of all the above cerebral areas during swallowing and tongue movements in the absence of RJM (Corfield *et al*., 1999; Sawczuk and Mosier, 2001).

In addition to the cerebral cortex, other areas of the central nervous system that have been associated with the experimental genesis of RJM in animals include the lateral hypothalamus, the antero-lateral or central nuclei area of the amygdala (Schärer *et al*., 1967; Lund and Dellow, 1971; Nakamura and Kubo, 1978; Sasamoto and Ohta, 1982), the basal ganglia (putamen of striatum, globus pallidus, substantia nigra), the thalamic reticular nuclei (also important in sleep genesis; see Section IV), the mesencephalic reticular formation, the pontine pyramidal tract, and red nuclei (Kawamura and Tsukamoto, 1960; Schärer *et al*., 1967; Lund and Dellow, 1971; Schärer, 1971; Hashimoto *et al*., 1989). In rabbits, stimulation of the hypothalamic 'defense attack area' facilitates the jaw-closing muscle reflex, which indicates that the trigeminal sensorimotor system is activated in aggressive behavior (Landgren and Olsson, 1977). In rats, projections from the central amygdaloid nuclei to the contralateral trigeminal motor nuclei, the parabrachial area, the supratrigeminal area, and the pontine reticular formation (Takeuchi *et al*., 1988) and, in monkeys, from the magnocellular divisions of basal nuclei of the amygdala and the CMA (Hatanaka *et al*., 2000) also support the interaction among reactive behavior (*e.g*., aggressive), trigeminal sensorimotor functions, and autonomic activities.

Stimulation of peripheral sensory receptors also influences RJM. For example, rubbing the oral mucosa and stimulation of periodontal mechanoreceptors increase jaw-closing activity during RJM (Lavigne *et al*., 1987; Morimoto *et al*., 1989; Lund, 1991; Komuro *et al*., 2001). The input from masticatory muscle spindles also influences the masticatory CPG (Lund, 1991; Kolta *et al*., 1995; Lund *et al*., 1998; Westberg *et al*., 2000). The role of peripheral factors in the onset and/or maintenance of sleep RMMA or SB, however, remains unclear.

Brainstem neuronal network in the genesis and control of RJM and RMMA

The role of neuronal networks in controlling masticatory movements has been extensively reviewed in this journal and elsewhere (Lund, 1991; Nakamura and Katakura, 1995; Lund *et al*., 1998, 1999; Nakamura *et al*., 1999). There are presently two prevailing models, that of Nakamura's group and that of Lund's group. Both models propose that cortico-bulbar inputs to contralateral brainstem structures first activate a relay in the medial pontomedullary reticular formation that eventually reaches the trigeminal motor nuclei and activates jaw-opening or jaw-closing muscles to produce jaw movements. The main distinction between the two models is the sequence of activation of various brainstem-reticular formation structures.

According to Nakamura's group, cortico-bulbar fibers tonically activate neurons of the paragigantocellularis (PGC) nuclei located ventrally in the medial reticular formation. These then activate a second group of neurons located dorsally in the gigantocellularis (GC) nuclei. These neurons fire rhythmically and project to neurons in the caudal nuclei reticularis parvocellularis (nPV) which project to and activate trigeminal motoneurons. In contrast, Lund and colleagues place the first relay in the medial reticular formation but at a slightly more rostral level in the nuclei pontis caudalis (nPC). They divide the nuclei into a ventral part, the neurons of which fire tonically to inhibit mandibular movement, and a dorsal part that maintains the motor rhythm (see Fig.). In their model, the CPG is made up of a rhythm generator in the nPC and a burst generator in areas immediately lateral to it, which include the supratrigeminal, intratrigeminal area, the main sensory nuclei, and the oralis subdivision of the trigeminal spinal tract nuclei. These areas contain most of the final-order interneurons and receive extensive input from nPC and from primary afferents. These neurons are therefore in an excellent position to integrate peripheral sensory information (from muscle, joint, teeth, mucosa, etc.) with rhythmic activity from the nPC to generate an efficient and well-adapted pattern of movement such as that which may be observed during mastication.

As described below, several of these brainstem reticular nuclei are also involved in sleep genesis and maintenance, while others are also important in respiration. Neuropharmacologically, several similarities are found. Acetylcholine (ACh), Adr, NA, DA, GABA, glutamate/N-methyl-D-aspartate (NMDA), glycine, 5-HT, and other neurochemicals have been reported to have a common influence (see Table 2). However, caution is needed when making a specific association between rhythmic movements and a given neurotransmitter, since receptors can be expressed differently (*e.g*., synthesis of 5 subtypes of DA receptor), have different targets of action (*e.g*., nigrostriatal or limbic neurons), and can also be co-localized with other neurochemicals (*e.g*., DA and 5-HT, in the trigeminal mesencephalic nuclei) (Liem *et al*., 1997).

(B) RESPIRATION

In a subject in the awake state, a tonic drive from the reticular activating system keeps respiratory cells excited. Reflexive (*e.g*., sneezing, coughing), voluntary (*e.g*., speaking or sighing), or reactive (*e.g*., hyperventilation due to anxiety) activities main-

TABLE 2
Neurochemicals Involved in Mastication Genesis or Sleep Motor Control (Most have an unknown action on sleep RMMA or SB)

	Mastication	Sleep
Acetylcholine (ACh)	• Increases cortical motor excitability (Liepert *et al.*, 2001) • Reduces oral tardive dyskynesia (OTD*) induced by DA	Major sleep-promoting projection fibers to activate glutamate and glycine/inhibitory neurons that induce REM muscle atonia (Siegel, 2000)
Adenosine	Role in hypothalamic oral aggressive/ defensive behavior (Nagy *et al.*, 1986; Amir *et al.*, 1997; Gottesmann, 1997)	Promotes deep sleep (SWA)/caffeine is opposite (Gallopin *et al.*, 2000)
Adrenaline (Adr) or noradrenaline (NA)	Facilitates RJM induced by glutamate: ↑ in SB? (Nakamura and Katakura, 1995; Sjöholm *et al.*, 1996; Amir *et al.*, 1997; Gottesmann, 1997)	NA triggers above ACh-induced atonia; promotes alertness/arousal (Gallopin *et al.*, 2000; Siegel, 2000)
Angiotensin	Facilitates DA-induced RJM (Gerstner *et al.*, 1989)	?
Calcium (Ca) channels	Synaptic activation (Soto-Trevino *et al.*, 2001)	Synaptic key event that contributes to GABA inhibition of arousal center/essential to sleep (Kandel *et al.*, 2000; Siegel, 2000)
Cholecystokinin (CCK)	Promotes rhythmic jaw movement (RJM) (Nishikawa *et al.*, 1985; Kojima *et al.*, 1992; Stoessl and Polanski, 1993)	Controversial effect (Pietrowsky *et al.*, 1990; Kapás *et al.*, 1991; Jones, 2000)
Dopamine (DA)	Promotes RJM and OTD DA_1 receptor = ++ agonist DA_2 receptors = + antagonist, - agonist DA_3 receptor = no effect (Gunne *et al.*, 1982; Lambert *et al.*, 1986; Johansson *et al.*, 1987; Koshikawa *et al.*, 1989; Spooren *et al.*, 1991; Lublin *et al.*, 1992; Lublin, 1995; Nakamura and Katakura, 1995)	Promotes alertness/arousal (*e.g.*, ventrotegmental area of hypothalamus) and is a major factor in the pathophysiology of PLMS (Jones, 2000; Montplaisir *et al.*, 2000)
GABA	• Facilitation of RJM (minor role) or inhibition of RMJ induced by DA • Twitches secondary to lack of inhibition (Gunne *et al.*, 1982; Lambert *et al.*, 1986; Johansson *et al.*, 1987; Cools *et al.*, 1989; Koshikawa *et al.*, 1989; Spooren *et al.*, 1991; Lublin *et al.*, 1992; de Beltrán *et al.*, 1993; Lublin, 1995; Nakamura and Katakura, 1995)	• Promote sleep onset and non-REM thalamo-cortical EEG pattern • In REM, it contributes to NA and 5-HT neuron inhibition that normally facilitates ACh action (Nitz and Siegel, 1997a,b; Gallopin *et al.*, 2000; Kandel *et al.*, 2000; Siegel, 2000)
Glutamate/NMDA	• Facilitates RJM/dorsal nPC. • Blocks phasic RJM/ventral nPO. • Facilitates jaw-opening motoneurons (Nakamura and Katakura, 1995; Lund *et al.*, 1998)	Involved in reticular activating/arousal
Glycine	Inhibition of jaw-closing motoneurons (Nakamura and Katakura, 1995; Lund *et al.*, 1998)	Responsible for motoneuron inhibition in REM = Atonia (Nitz and Siegel, 1997a,b; Gallopin *et al.*, 2000; Kandel *et al.*, 2000; Siegel, 2000)
Histamine	Facilitates RJM	Promotes alertness/arousal (Jones, 2000)
Hypocretin/orexin	Putative facilitation of jaw-opening/jaw-closing motoneurons (Fung *et al.*, 2001)	Promotes alertness/arousal but also promotes REM (Kilduff and Peyron, 2000)

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	Mastication	Sleep
Serotonin (5-HT)	Facilitates RJM; SSRI increases bruxism; 5-HT 2c receptor involved in RJM and CPG facilitation (Lund, 1991; Nakamura and Katakura, 1995; Eberle-Wang *et al.*, 1996; Fornal *et al.*, 1996; Lavigne and Manzini, 2000; Di Matteo *et al.*, 2001)	Promotes sleep onset: 5-HT_2 and 1_A; decreases activity in non-REM and REM (Seifritz *et al.*, 1997; Jacobs and Fornal, 1999; Landolt *et al.*, 1999; Gallopin *et al.*, 2000; Kandel *et al.*, 2000; Siegel, 2000)
Leukotriene (IL and PGD_2)	?	Sleep-promoting (Jones, 2000)
Melatonin	?	Sleep-promoting
Opioids	Putative depressor of RJM	Sleep-promoting and reduces gigantocellularis—glycine inhibition of motoneurons during sleep (Jones, 2000)
Vasointestinal peptide (VIP) or Substance P	? Facilitates RJM	Promotes arousal (Jones, 2000)

* Abbreviations: CPG, central pattern generator; IL, interleukin; OTD, oral tardive dyskinesia; PGD_2, prostaglandin D_2; PLMS, periodic limb movement during sleep; REM, rapid eye movement (a sleep stage); RJM, rhythmic jaw movement; SWA, slow wave activity; SB, sleep bruxism; and ?, unknown.

tain breathing function. There are two main respiratory patterns, a sustained-tonic inspiratory/excitatory one and a phasic inspiratory/expiratory one. Both are under the influence of central (*e.g.*, brainstem neurons) and peripheral feedback (*e.g.*, chemoreceptors) (Orem and Kubin, 2000). At the central level, respiration is a rhythmic activity controlled by a network of neurons, also termed the CPG, located in the caudal brainstem.

The first group of neurons in this network is termed the dorsal respiratory group, which is part of the nuclei tractus solitarius (NTS); it receives input from glossopharyngeal and laryngeal structures. The NTS neurons are responsible for inspiration/expiration and project to the phrenic and intercostal motoneuron pools in the spinal cord. The second group of rhythmic respiratory cells is located in the ventral brainstem area. The neurons form a column that extends from the retrofacial nuclei to the first cervical segment that includes the Bötzinger complex, the nuclei ambiguus, and nuclei retroambigualis. These neurons are important in the genesis of inspiratory/expiratory rhythm. They also contribute to the maintenance or modification of respiratory frequency (Gray *et al.*, 1999). In addition, they have a role in maintaining airway patency, since the axons originating in the nuclei ambiguus innervate the muscles of the upper pharynx and larynx (Orem and Kubin, 2000). The upper airway muscles are also innervated by trigeminal, glossopharyngeal, vagus, and hypoglossal motor axons. The harmonious integration of respiratory, swallowing, and masticatory CPG activities, essential to the prevention of food aspiration, seems to be possible through a recently recognized ventrolateral medulla region. Chemical stimulation, by glutamate, of an area, the intratrigeminal region, receiving inputs from the trigeminal spinal nuclei and NTS nuclei seems to trigger central apnea (Chamberlin and Saper, 1998). Furthermore, facial and hypoglossal motor roots discharge in synchronized rhythm, as was observed in an *in vitro* slice preparation containing the pre-Bötzinger complex and ventrolateral medulla (Jacquin *et al.*, 1999).

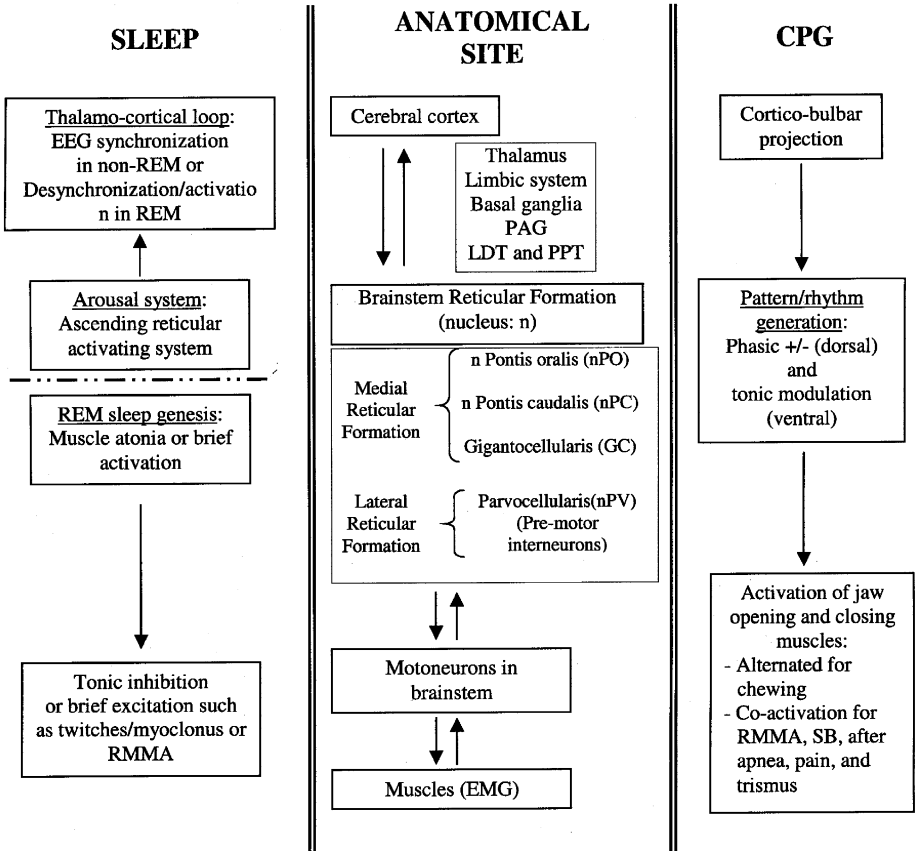
A third respiratory-related group consists of chemosensitive neurons (*e.g.*, some are excited by CO_2) located in the ventral medullary surface of the brainstem, the pontomedullary reticular formation, and its PGC lateralis area, a structure also associated with control of RJM (see Section III-A). Interestingly, local reversible cooling of the latter structure evokes apnea. Finally, the pontine group of respiratory neurons, also termed the pneumotaxic center, has an important role for switching between respiratory phases but is less critical in the genesis of respiratory rhythm (Sawczuk and Mosier, 2001). It includes respiratory neurons in the pons, in the Kolliker-Fuse subdivision of the parabrachial nuclei; it receives afferent input from the central neural structures involved in autonomic, emotional, and somatosensory functions, which further suggests a role for the pneumotaxic center in respiratory changes associated with emotion, stress, pain, etc. (Frysinger *et al.*, 1988).

The respiratory CPG is also under the influence of the neurons' baseline membrane potential to generate the respiratory rhythm of neurons from the pre-Bötzinger complex (Koshiya and Smith, 1999). These neurons are quiet when they are hyperpolarized at -65 mV and show sustained oscillating activity at potentials above -45 mV. The genesis of the respiratory rhythm depends on a high extracellular potassium (K+) concentration. In the pre-Bötzinger complex level, the rhythmic pattern of respiratory neurons can be facilitated by neurokinins (*e.g.*, substance P) and inhibited by opioids (*e.g.*, enkephalin) (Gray *et al.*, 1999, 2001). Excitatory amino acids acting at non-NMDA receptors, as well as at 5-HT and NA brainstem neurons, have also been reported to influence respiratory motoneurons and hypoglossal motoneurons (Orem and Kubin, 2000; Sawczuk and Mosier, 2001).

Most neurochemicals (see Table 2) involved in the genesis of mastication and sleep motor activity have a role in respiration (Sessle and Henry, 1989; Horner, 2001); their description is beyond the scope of this review. The multiplicity of neurochemicals and receptors is notable, so caution is again recommended before one draws conclusions about the role of a specific neurochemical, since, for example, there are at least 14 molecularly defined 5-HT receptor subtypes and 9 different subtypes from the two pharmacological classes of adrenoceptors (Alexander *et al.*, 2001).

TABLE 3

Brainstem Reticular Formation: Role in Sleep (non-REM and REM) and in Jaw Movement Genesis/Central Pattern Generator (CPG*)



* Abbreviations/symbols: +, excitation; -, inhibition; EEG, electroencephalographic; EMG, electromyographic; CPG, central pattern generator; REM, rapid eye movement; and RMMA, rhythmic masticatory muscle activity.

(IV) Sleep and Masticatory Muscle Activity

NON-REM SLEEP AND MOTOR ACTIVATION

A marked shift in the activity of the thalamo-reticular neuronal network is observed during the transition from wakefulness to drowsiness to the first non-REM sleep period and sleep stages 1 and 2. During wakefulness, arousal and maintenance of muscle tone are facilitated and maintained through the release of ACh from midbrain reticular laterodorsal tegmental (LDT) and pedunculopontine (PPT) nuclei, of histamine (H), dopamine (DA), and orexin from the posterior hypothalamus, and, to a certain extent, of NA from the locus ceruleus and 5-HT from the raphe nuclei (Table 2). Neurons in these cerebral structures control the thalamic and cortical cells associated with arousal. However, at sleep onset (*e.g.*, from drowsiness to stages 1 and 2), a reversal of such 'activation' is needed. It has been proposed that the inhibitory neurotransmitter GABA can reduce the above influences. The GABAergic neurons of the thalamic nuclei reticularis induce hyperpolarization (a reduction in excitability) of cortical cells that allows low-threshold Ca++ current channels to be activated for a brief period (*e.g.*, producing a burst of action potentials). The cortical cells then maintain a synchronous EEG discharge pattern. This sequence of events is responsible for the synchronization of the cortical neurons, the appearance of EEG spindles (7-14 Hz) discharged from thalamo-cortical cells, and of the EEG slow-wave activity (SWA) of sleep stages 3 and 4 that, together, characterize non-REM sleep (Gallopin *et al.*, 2000; Rechtschaffen and Siegel, 2000; Steriade, 2000).

Sleep stages 3 and 4, or deep non-REM sleep, are characterized by a low responsiveness to external inputs (*e.g.*, sound, innocuous and noxious stimulations) as well as endogenous ones (*e.g.*, respiratory disruption such as apnea). The EEG traces show a slow rhythmic discharge (1-4 Hz) with large-amplitude waves. This activity is due to a more active synchronization of the thalamo-cortical neuronal network, which is also important for maintaining sleep continuity (Steriade, 2000). Specifically, deep sleep is characterized by a long neocortical neuronal hyperpolarization where K+ currents and GABAergic inhibitory interneurons further hyperpolarize the thalamo-cortical neurons. This de-activates Ca++ channels, which, once open, allow the cells to fire bursts of Na+ spikes that ride on top of the Ca++ spikes. As a consequence, a more powerful cortical activation projects back to the thalamus and, on its way, activates the GABAergic interneurons, allowing the cycle to recommence (Timofeev *et al.*, 2001).

During non-REM sleep, the neuronal activity that preserves sleep continuity is disrupted by the occurrence of spontaneous motor events such as SB or RMMA and PLM (*e.g.*, movement arousals). In non-REM sleep, there is a general reduction in muscle tone in comparison with wakefulness. This could result from a reduction in the cortico-bulbar drive, as seen by the lower discharge pattern of pyramidal tract (cortico-spinal) neurons from the motor cortex (Evarts, 1963) and/or tonic hyperpolarization of the masseter motoneurons, making them less excitable (Chase and Morales, 2000), or from a reduction in arousal-driven monoaminergic tone as described above. However, most of the spontaneous motor activity, such as PLM, RMMA, and oromandibular myoclonus, occurs in the light non-REM sleep stages 1 and 2 (Kato *et al.*, 1999; Lavigne and Manzini, 2000; Montplaisir *et al.*, 2000; Saber *et al.*, 2002). Putative mechanisms that could contribute to these sudden motor activations could be associated with: (1) a sudden decrease in activation and/or incomplete inhibition of Ca++ channels normally associated with the thalamo-cortical synchrony described above; (2) transient arousal, since over 80% of RMMA and SB has been observed with CAP and with a rise in brain activity and heart rate (Macaluso *et al.*, 1998b, and/or Kato *et al.*, 2001a); or (3) an increase in the influence from substances associated with arousal, including ACh, 5-HT, NA, H, and hypocretin/orexin (Kilduff and Peyron, 2000; Fung *et al.*, 2001; Hang *et al.*, 2002; Mignot *et al.*, 2002; Rye, 2003). So far, the exact mechanisms

responsible for sleep RMMA and SB, and the sudden motor activation in non-REM sleep, remain unknown.

REM SLEEP AND MOTOR ACTIVATION

The high frequency and desynchronized EEG activity characteristic of REM sleep resemble the state of being awake. As described in Section II, the heart rate is also highly variable and rapid, and phasic eye movements are observed. Paradoxically, REM sleep is associated with a powerful "atonia" (or hypotonia) of limb and jaw muscles. The mechanism behind REM sleep is similar to that underlying wakefulness. At the onset of REM sleep, EEG spindle and SWA activities of non-REM sleep are blocked by the re-activation of ACh influences from the midbrain reticular nuclei, PPT and LDT. ACh depolarizes the thalamic nuclei reticularis neurons and, by doing so, prevents activation of the low-threshold Ca++ channels. The previously described release of substances related to sleep and muscle tone modulation, such as 5-HT from the nuclei raphe, NA from the locus ceruleus, and H from the posterior hypothalamus, is further reduced. Interestingly, during REM sleep, neurons related to jaw muscle activity, the nPO and nPC (see Section III-A for abbreviations), discharge at high frequency, just as they do in awake aroused states. The excitation of the nGC and nPV neurons has also been associated with the phasic eye movements of REM sleep (Jones, 1990; Gottesmann, 1997; Chase and Morales, 2000; Siegel, 2000). The nPC contributes to muscle atonia through a GABA, ACh, glutamate, and glycine sequence of inhibition-excitation that reduces motoneuron excitability and thus decreases muscle tone. Two major pathways seem to be involved in the atonia-hypotonia of REM sleep. The first pathway includes the pontine cholinergic neurons that activate glutamatergic neurons in the medial medullary reticular formation. These neurons in turn activate inhibitory glycinergic neurons that reduce motoneuron activity. In the second pathway, GABAergic neurons silence the 5-HT and NA neurons that were maintaining an excitatory drive on motoneurons (Rechtschaffen and Siegel, 2000).

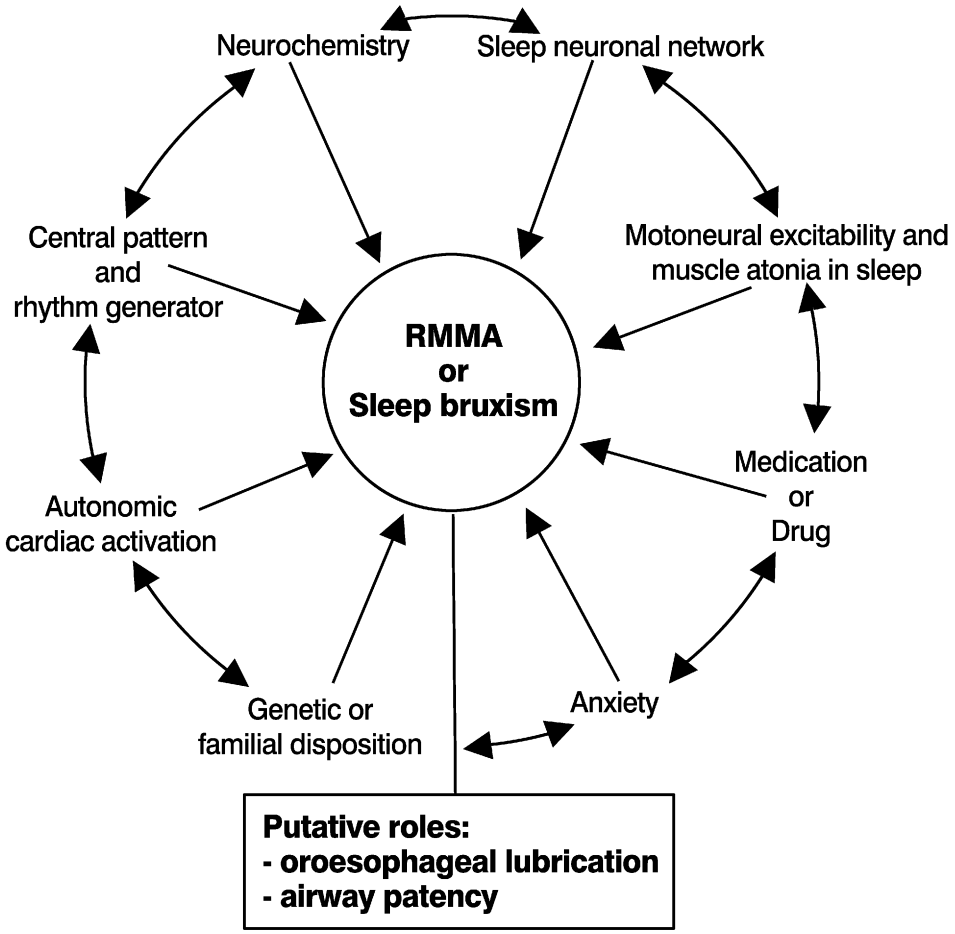


Figure. RMMA and sleep bruxism result from the integration of various influences.

Our understanding of RJM physiology and its relation to sleep has been advanced by studies on oro-facial motoneuron properties in animals. It has been reported that the membrane potential of the jaw-closing motoneurons is hyperpolarized during sleep, changing from ≈-55 to -60 mV during wakefulness to below -60 mV during non-REM sleep to less than -75 mV during REM sleep (Chase and Morales, 2000). The decline in membrane potential reflects a decrease in trigeminal motoneuron excitability, although a sudden and transient period of increased excitability has been observed both in animal cellular recordings (Nakamura *et al*., 1984; Chase and Morales, 2000) and in EMG recordings in humans (Kato *et al*., 1999; Lavigne *et al*., 2001c). A sudden change in trigeminal motoneuron excitability during REM sleep, produced by neurons in the dorsal GC, nPO, and nPV, is one of the mechanisms that could reduce the inhibitory influences associated with muscle atonia (see Table 3) (Castillo *et al*., 1991; Kohlmeier *et al*., 1996; Gottesmann, 1997; Chase and Morales, 2000). It has also been suggested that the sudden interruption of the powerful tonic inhibitory action on motoneurons during REM sleep could be attenuated by the excitatory influences from the neurons involved in arousal (*e.g.*, the one releasing NA, 5-HT, H) (Gottesmann, 1997; Jacobs and Fornal, 1999; Chase and Morales, 2000; Rye, 2003). For example, the administration of NA, Adr, and DA in the region of the locus ceruleus selectively inhibits the "atonia" that normally occurs in REM sleep (Crochet and Sakai, 1999).

SLEEP AND MUSCLE SPINDLE ACTIVITY

As described above in Section III-A, mastication can be triggered by a voluntary motor command from the cortex or by peripheral inputs. It is well-known that trigeminal motoneurons are influenced by inputs from jaw muscle spindle afferents that carry information about muscle length, jaw position (open or closed), and, to a certain extent, tension (Lund, 1991; Komuro *et al*., 2001). The jaw muscle spindles are either primary endings responding mainly to dynamic stretch, or secondary

endings responding mainly to jaw displacement. The jaw muscle spindle afferents have their cell bodies in the trigeminal mesencephalic nuclei and synapse on alpha motoneurons in the trigeminal motor nuclei. Fibers containing GABA, 5-HT_2, DA, SP, CCK, VIP (vasointestinal peptide), enkephalin, and neuropeptide Y have been detected in the trigeminal mesencephalic nuclei, and specific receptors for GABA, 5-HT_2, DA_1, and DA_2 neurotransmitters have also been reported (Copray *et al*., 1990; Kolta *et al*., 1993; Liem *et al*., 1997; Lund *et al*., 1998) (see Table 2). To our knowledge, jaw muscle spindle activity, unlike that of cat limb muscles (*e.g*., from extensors gastrocnemius, soleus, or flexor tibialis muscle activity), has not been specifically studied during sleep. However, it is known that limb muscle spindle activity decreases and becomes irregular in non-REM sleep in comparison with wakefulness; this activity decreases during REM sleep where muscle "atonia" is present (Kubota *et al*., 1967).

Sleep oro-facial muscle reflexes and cortical excitability

The study of jaw reflexes is also a rich source of information on trigeminal motor excitability during sleep. In animals, it was first observed that the digastric (jaw-opening) reflex induced by inferior dental nerve stimulation is facilitated during non-REM sleep (*e.g*., an increase in amplitude) and is almost completely depressed during REM sleep (*e.g*., no reflex response observed) in comparison with the awake state (Chase, 1970). These findings are surprising, since it was shown that the leg tibialis flexor reflex was slightly depressed in non-REM sleep, while it was 'strikingly' depressed in REM sleep (Marchiafava and Pompeiano, 1964). However, some of these observations have recently been challenged, since it was found that the amplitude of the jaw-opening reflex is not different between wakefulness and non-REM sleep; importantly, the observed suppression in REM sleep was confirmed (Chase, 1970; Inoue *et al*., 1999). The amplitude of the opposite reflex, the masseteric jaw-closing one, was not different between wakefulness and non-REM sleep, but it was also reduced during REM sleep (Inoue *et al*., 1999). The suppression of the masseteric reflex during REM sleep was shown to be due to a post-synaptic glycine action (Soja *et al*., 1987). In humans, to our knowledge, the trigeminal reflex has not been tested during sleep.

The use of trigeminal and facial reflex testing is impossible during sleep, since it requires voluntary contraction of the jaw muscles (Macaluso *et al*., 1998c, 2001; Cruccu and Deuschl, 2000). Furthermore, although the integrity of trigeminal cortico-motoneuronal projections and their excitability may be tested in human subjects by the use of transcranial stimulation (TCS) (Cruccu *et al*., 1989), a voluntary contraction of the jaw muscles is also mandatory for obtaining a TCS-evoked motor response, a condition impossible to maintain while the subject is asleep. As previously noted, TCS may also interfere with sleep continuity (Cruccu *et al*., 1989; Smith *et al*., 1992).

(V) Pathophysiology of Sleep Bruxism

Exploration of the pathophysiology of SB covers most areas of biomedical sciences, and no single mechanism is likely to explain it (Table 1; Fig.). In terms of etiology, although stress and psychosocial variables have been associated with SB (Glaros and Rao, 1977; Kristal, 1979; Harness and Peltier, 1992; Biondi and Picardi, 1993; Hartman, 1994; Kampe *et al*., 1997), a recent study failed to show a relation between awake stress and EMG changes in sleep (Pierce *et al*., 1995). The strongest agreement among several authors is that SB patients present an anxious personality (not an anxiety disorder) and are more task-oriented (*e.g*., focused on successful performance) in comparison with normals (Kristal, 1979; Pingitore *et al*., 1991; Biondi and Picardi, 1993; Hartman, 1994; Bader *et al*., 1997; Kampe *et al*., 1997; Major *et al*., 1999).

As for risk factors, smoking is considered as a modest risk for SB (Lavigne *et al*., 1997). Age represents a dominant factor; SB declines from childhood to old age (Lavigne and Montplaisir, 1994; Laberge *et al*., 2000). No gender difference has been noted for SB. However, the original hypothesis that SB could be associated with a familial predisposition has been recently supported by studies with twins. No genetic inheritance pattern has so far been documented (Reding *et al*., 1966; Lindqvist, 1974; Hublin *et al*., 1998).

A critical review of the role of occlusion in SB pathophysiology is beyond the scope of this paper. The current literature on the genesis of SB, as described below, supports the view that SB and tooth-grinding are among the last events in the sequence of sudden brain and cardiac activations termed 'micro-arousal during sleep' (Macaluso *et al*., 1998b; Kato *et al*., 2001a).

RMMA and SB, and sleep architecture

Sleep organization in SB patients and in non-tooth-grinding subjects with RMMA is usually normal in terms of sleep duration, sleep efficiency (estimation of time asleep over time in bed), and sleep stage distributions (Lavigne *et al*., 1996, 2001c). Most SB episodes (60-80%) occur in light non-REM sleep (Macaluso *et al*., 1998b; Saber *et al*., 2002). In the literature, the presence of high-amplitude EEG positive and negative signals, termed K-complexes, is considered a marker of transient EEG activation (see Section II). It has been previously associated with SB (Reding *et al*., 1968; Satoh and Harada, 1973). However, in a recent analysis comparing SB and controls, it was noted that SB patients had significantly fewer K-EEG events than normals (Lavigne *et al*., 2002).

Sleep micro-arousal, as defined in a previous section, is an unconscious and transient three- to 10- or 15-second burst of brain EEG activity, alone or sometimes with an increase in heart rate and muscle tone. Although the incidence of micro-arousal (# events/hr of sleep) is moderately correlated with the high frequency of masticatory muscle activity, it is the magnitude (*e.g*., a more rapid onset in heart rate, a bigger rise in EMG activity, and a forceful tooth contact with grinding) of micro-arousal that seems to distinguish SB patients from normals (Satoh and Harada, 1973; Macaluso *et al*., 1998b; Kato *et al*., 2001a; Lavigne *et al*., 2001c). This is consistent with the observation that most SB episodes occur in a period of intense EEG and autonomic activation that has been termed a 'cyclic alternating period' (CAP) (see Section II) (Terzano and Parrino, 1993, 2000; Macaluso *et al*., 1998b). Interestingly, when SB episodes occur with an active CAP phase, very few K-complexes are observed (Macaluso *et al*., 1998b).

An acceleration in cardiac rhythm, also a sign of an autonomic-cardiac sleep arousal, has been previously observed in relation to SB episodes (Reding *et al*., 1968; Satoh and Harada, 1973; Sjöholm, 1995; Ikeda *et al*., 1996; Bader *et al*., 1997). Although the rise in heart rate associated with SB is important, it is not specific, since a similar increase ($\approx$ 25%) is also observed with RMMA episodes in normals (Kato *et al*., 2001a).

However, in comparison with normals, SB patients do show a more rapid onset of heart rate (HR) increase (Kato *et al*., 2001a). Although 90% of RMMA and SB episodes have been observed in association with EEG- and EMG-related micro-arousal, a clear sequence of physiological activation occurs before the onset of 80% of these episodes. In the four-second period before RMMA, there is first a clear increase in the power of EEG activity, followed by a rise in heart rate. Again, this increase in heart rate is not unique to RMMA and SB, since it has been observed with another periodic motor manifestation during sleep, *i.e*., periodic limb movements (PLM) (Sforza *et al*., 1999; Bader and Lavigne, 2000). The above evidence suggests that SB episodes are closely related to the transient EEG cardiac and EMG activations that are part of sleep micro-arousal (Bader and Lavigne, 2000; Lavigne and Manzini, 2000).

The proposal that SB and RMMA are associated with sleep arousal (Satoh and Harada, 1973) is further supported by the observation that tooth-grinding and RMMA can be evoked experimentally through manipulations that trigger micro-arousal (Reding *et al*., 1968; Macaluso *et al*., 1998a,b; Bader and Lavigne, 2000; Lavigne and Manzini, 2000; Sjöholm *et al*., 2000). In humans, auditory or photo-optic flash stimulation triggers tooth-grinding episodes (Satoh and Harada, 1973). In a recent controlled study in which sleep arousal was induced by auditory or vibrotactile stimuli, 11% of experimental sleep arousals were followed by RMMA, and 71% of these were associated with tooth-grinding in SB patients (Kato *et al*., 2002, 2003b).

SB AND NEUROCHEMICAL INFLUENCES

Among the neurochemicals associated with rhythmic jaw movements (RJM; see Table 2), the first substance reported to influence SB was L-dopa (a precursor of dopamine [DA]), adrenaline (Adr), and noradrenaline (NA)) (Magee, 1970). However, this observation was made in only one Parkinsonian patient who presented tooth-grinding secondary to the use of medication. The finding was not conclusive, since RMMA and tooth-grinding were not recorded before the onset of Parkinsonian signs and symptoms. It is uncommon that, following the discovery of a given disorder, the patient or family recognizes unusual activity of which they were previously unaware. Since Parkinson's disease is a dramatic disease associated with a progressive neuro-degenerative process of the basal ganglia (Levy and Cummings, 1999), our research group wanted to determine whether young adults with severe SB could have early changes in DA binding at the striatal level. We used a brain imaging technique with a DA-type 2 receptor marker, Iodine-123-Iodobenzamide (IBZM). Although we found a side-to-side asymmetry in striatal DA binding, we did not observe early evidence of DA changes in SB patients in comparison with normal subjects (Lobbezoo *et al*., 1997b). Interestingly, in SB patients with no medical or psychological disorder or using medication, a controlled study with L-dopa showed a modest ($\approx$ 30%) but significant reduction in SB-related motor activity (Lobbezoo *et al*., 1997a). The specificity of DA in the genesis of SB remains equivocal, because an increase in tooth-grinding was reported in schizophrenic patients treated with a DA antagonist (*e.g.*, haloperidol) (Micheli *et al*., 1993), and a recent controlled study with a modest DA agonist (*e.g.*, bromocriptine) did not reveal any effect in SB patients (Lavigne *et al*., 2001d).

Propranolol, a catecholamine beta-adrenergic receptor blocker, has been reported in one open study to reduce tooth-grinding in patients using neuroleptics (Amir *et al*., 1997). A similar finding was observed in a single SB patient without any history of neuroleptic use (Sjöholm *et al*., 1996). Propranolol provides an interesting avenue for investigating the role of catecholamines in SB (Lobbezoo *et al*., 1997a), but at this time it would be premature to recommend its clinical use for SB management, since ongoing controlled double-blind studies have not yet been concluded. Moreover, the observations that propranolol can both reduce sleep quality and worsen sleep disorders (*e.g.*, apnea, insomnia, RBD; see Section I) further indicate the need for a conservative approach (Lavigne and Manzini, 2000).

The role of serotonin (5-HT) in SB pathophysiology is also not clear. In several case reports, the administration of selective 5-HT re-uptake inhibitors (SSRI), such as fluoxetine, sertraline, fluvoxamine, and paroxetine, has been associated with tooth-clenching or tooth-grinding (Ellison and Stanziani, 1993; Por *et al*., 1996; Gerber and Lynd, 1998). Again, given the absence of a validated past history of tooth-grinding and any polygraphic investigation for oro-motor quantification that confirmed or ruled out SB, a strong association of cause and effect cannot be drawn from these studies. Moreover, the use of either a 5-HT precursor (tryptophan) or a modest but classic selective re-uptake blocker (amitriptyline) failed to exacerbate or attenuate SB (Etzel *et al*., 1991; Mohamed *et al*., 1997; Raigrodski *et al*., 2001).

The study of SB pathophysiology based on clinical reports or controlled drug trials has not yet provided a simple neurochemical explanation. Moreover, most neurochemical substances used so far have a cross-affinity with other receptor families. For example, bromocriptine presents a cross-affinity for DA and Adr receptors (Jackson *et al*., 1988), and propranolol for Adr and 5-HT receptors (Hindle, 1994). In addition, several neurochemical substances have been associated with RJM (Table 2), and in the absence of controlled studies, it is premature to associate these with SB pathophysiology.

(VI) Putative Role for Oro-motor Activation during Sleep

As described in Section I, several oro-facial motor activities have been observed during sleep, such as sustained clenching and myoclonus (Lavigne and Manzini, 2000; Kato *et al*., 2001b). Moreover, close to 40% of the oro-facial activities observed in moderate to severe young SB patients may not be related to bruxism (*e.g.*, could be related to swallowing, grunting, sighing, or talking during sleep) (Lavigne and Manzini, 2000; Kato *et al*., 2001b). The most frequent oro-facial motor activity observed during sleep is RMMA that is classified as SB when it manifests as tooth-grinding. As previously discussed, the RMMA frequency is three times higher in SB patients than in normal sleepers, 70% more masseteric bursts *per* episode are observed, and, while EMG burst duration is 40% shorter, burst amplitude is 60% higher (Lavigne *et al*., 2001c). This suggests that, in SB patients, RMMA contractions show more powerful activity. Moreover, as previously discussed, RMMA is frequently coincident with sleep arousals. Despite the high frequency of motor activity in SB patients, they are, in general, good sleepers and show no disruption in the density of SWA, which is a marker of deep sleep, and they may even have fewer K-complexes than normals (Lavigne *et al*., 2002). The frequently asked question, then, is: Why does RMMA or SB occur? Do these sudden oral motor activations have any role? Two major suggestions are advanced in this review. They are based on indirect evidence but have at least the merit of suggesting fruitful avenues for research: (1) a role in

lubricating the upper alimentary tract during sleep, and (2) a role in improving airway patency during sleep (see Fig.).

Salivation and sleep

During wakefulness, a higher rate of salivary flow occurs during chewing, biting, or talking than during rest (Anderson *et al*., 1996; Anderson and Hector, 1987; Hector and Linden, 1987; Jensen Kjeilen *et al*., 1987; Losso *et al*., 1997; Scott *et al*., 1998). During the day, salivary flow rate is also subject to circadian influences; it is higher in the afternoon than in the morning (Borgeat *et al*., 1984). Salivary flow rate is also very low during sleep compared with daytime activity, although the rate in different sleep states is not known (Gemba *et al*., 1996). Compared with the awake state, swallowing is also lower in sleep, and is lower in deep non-REM or REM sleep stages than in non-REM light sleep (Lichter and Muir, 1975; Castiglione *et al*., 1993).

We have recently proposed that, during sleep, RMMA could contribute to triggering the release of saliva to protect, through a lubricating action, the integrity and health of the upper alimentary tract (*e.g*., oro-esophageal structures) (Thie *et al*., 2002). Currently, it is not easy to conduct research assessing the differences in salivary flows during sleep between normals and SB patients, since it is obviously impossible to make repetitive measures of total saliva volume over a given time without disrupting sleep itself (*e.g*., use of a collector tube or asking the subject to spit). However, it is possible to assess the difference in swallowing rates during sleep by the use of a non-invasive neck collar strain gauge that measures hyoid bone movement (*e.g*., laryngeal displacement) as an indicator of swallowing, in parallel with surface EMG recordings of suprahyoid and masseter activity (Nederkoorn *et al*., 1999; Ertekin *et al*., 2001). This technique also allows natural saliva swallowing to be clearly distinguished from experimental water swallowing (Perlman *et al*., 1999; Ertekin *et al*., 2001). Using such methodology, with video recordings focused on neck and jaw movements, we have observed that close to 60% of sleep RMMAs are associated with swallowing in both normal and SB patients (Miyawaki *et al*., 2003, accepted). Therefore, it appears that swallowing may, like RMMA, be part of the sleep arousal activation of the brain, heart, and muscles.

Jaw position and muscle activity with airway patency

During sleep, a general reduction in airflow is observed, due to a loss in voluntary control of respiratory muscles, a decrease in ventilatory responses to low oxygen (hypoxemia), and high carbon dioxide levels (hypercapnia) (Douglas, 2000). These two responses are lower in non-REM sleep than in wakefulness and are even lower in REM sleep. The activity of muscles maintaining an upper airway patent (*e.g*., geniohyoid, genioglossus, levator veli palatine) is also reduced from wakefulness to non-REM sleep and even further during REM sleep (Carlson *et al*., 1994; Krieger, 2000). All these events contribute to reduction in airway patency during sleep.

A change in jaw position (*e.g*., open and retruded) with the above reduction in muscle activity (contributing to tongue retrusion with reduction in oropharyngeal opening during sleep) could explain the reduction in airway patency (Krieger, 2000; Lowe, 2000). The mandibular vertical opening of normal subjects increases from 0-2.5 mm for 80% of the time during quiet wakefulness to 0-0.5 mm for 90% of the time in sleep stage 2, to 2.5-10 mm for 75% of the time in sleep stages 3 and 4 and for 60% of the time in REM sleep (Miyamoto *et al*., 1998). In REM sleep, the vertical opening is over 10 mm for 6% of the time. It has been suggested that, in apneic patients, the mandible is retruded during sleep apnea (Hollowell and Suratt, 1991). However, it remains to be proven whether lower jaw retrusion in sleep is the cause, or rather the effect, of upper airway disturbance. It should also be noted that these last two studies used recording systems that could have restrained protrusive (forward) and retrusive (backward) jaw movements as well as vertical opening. Nonetheless, it is clear that jaw muscle tone does change during sleep. In comparison with wakefulness, the EMG activity of jaw-opening muscles in normal subjects (*e.g*., non-apneic) is reduced by three times during non-REM sleep and is eight times lower during REM sleep (Kato *et al*., 2003b, submitted). The EMG activity of the jaw-closing muscles is also reduced from sleep onset and remains seven times lower (in the absence of RMMA or SB) than during wakefulness over all sleep stages.

One of the characteristics of the pattern of EMG contractions in RMMA, for both normals and SB patients, is the co-activation of both jaw-opening and jaw-closing muscles (*e.g*., both are simultaneously active) (Lavigne *et al*., 1996, 2001b; Kato *et al*., 2001a). This co-activation pattern, however, is not unique to SB, since it has been previously documented in animals and humans during experimental or clinical pain and with post-operative jaw muscle trismus, a state with increased arousal/vigilance (Greenfield and Moore, 1969; Stohler *et al*., 1985; Yu *et al*., 1995; Cairns *et al*., 1998). Interestingly, when ventilation resumes following an episode of sleep apnea, in parallel to sleep arousal, a co-activation of jaw-opening, jaw-closing, and other muscles (*e.g*., genioglossus) associated with upper airway patency has also been observed (Hollowell and Suratt, 1989, 1991; Yoshida, 1998).

The putative role of RMMA in airway patency during sleep is also supported by the following observations. Again, over 80% of RMMAs are associated with sleep micro-arousal-responses (Macaluso *et al*., 1998b; Kato *et al*., 2001a), which could be associated with an increase in activity (over 150%) of the diaphragmatic muscle and in muscles (*e.g*., genioglossus and levator veli palatini) that dilate the upper airway, together with a rise in inspiratory flow and a reduction in upper airway resistance (Carlson *et al*., 1994; Macaluso *et al*., 1998b; Krieger, 2000). Moreover, animal studies have shown that, during anesthesia, a co-activation of tongue protruder (genioglossus) and retruder (styloglossus, hyoglossus) muscles also contributes to the prevention of pharyngeal collapse during inspiration (Fuller *et al*., 1998, 1999). This hypothesis needs to be assessed in SB patients by recordings of EEG and EMG and of respiratory variables (*e.g*., air flow, CO_2, chest belt, pharyngeal probe).

(VII) Conclusions and Future Research Directions

Although sleep is associated with a reduction in muscle tone, spontaneous rhythmic masticatory muscle activity, known as RMMA, is observed once or twice *per* hour in 60% of normal subjects. The RMMA is more frequent in SB patients who, in addition, grind their teeth and could complain of jaw muscle pain. Most of the RMMA episodes, in both normals and SB patients, are observed in non-REM light sleep stages 1 and 2. Recent evidence supports the view that SB is related to anxiety and is secondary to sleep arousal, which is defined as a tran-

sient increase in brain electrical activity and heart rate that precedes a tooth-grinding episode. In the awake state, voluntary rhythmic jaw activity is controlled by a brainstem CPG consisting of a neuronal network that produces alternate jaw-opening and jaw-closing movements. In addition, chewing has to be coordinated with food bolus localization, tongue position, swallowing, and respiration, so that feeding is possible without aspirating the food bolus into the airway. During sleep, the sudden activation of the jaw muscles is frequently associated with RMMA or SB, and with a return of airway patency after an apnea. Based on this review, the following themes are suggested for further research on the neurobiological mechanisms underlying RMMA and SB:

(1) Since over 90% of RMMA and SB events are associated with sleep EEG and cardiac micro-arousal during sleep, it remains unknown whether RMMA during non-REM sleep results from a sudden withdrawal of influences from the autonomic nervous system that reduce heart rate (*e.g.*, the dominant non-REM sleep parasympathetic influences) or from a sudden and transient rise in sympathetic dominance. This hypothesis is being tested in our laboratory.

(2) Although a sudden and rhythmic activity in jaw-opening and jaw-closing muscles during sleep has been observed in both normals and SB patients, several questions remain, such as: Do the CPG neuronal networks responsible for chewing and swallowing during wakefulness remain active during sleep? What is the level of jaw muscle spindle and motoneuron excitability during non-REM sleep in humans, the period during which most RMMA and SB episodes are observed?

(3) Most SB episodes seem to be associated with swallowing, but it remains to be established whether one function of RMMA is to facilitate upper alimentary tract lubrication during sleep.

(4) The co-activation of the jaw-opening and jaw-closing muscles is not unique to sleep RMMA and SB. It is also observed in certain pain states and at the end of a period of sleep apnea with the return of ventilation and airway patency. It remains to be documented whether RMMA contributes to the modification of the tongue and jaw positions and modification of airway patency during sleep.

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