



## Review article

## The neurophysiological basis of bruxism

Andrisani Giovanni <sup>a,b,\*</sup>, Andrisani Giorgia <sup>b</sup><sup>a</sup> Matera, via della Croce 47, Italy<sup>b</sup> Ezelsveldlaan 2, 2611 rv, Delft, the Netherlands

## ARTICLE INFO

## Keywords:

Bruxism  
 Mesencephalic trigeminal nucleus  
 Rhythmic masticatory muscle activity  
 Ventrolateral preoptic nucleus

## ABSTRACT

Mesencephalic trigeminal nucleus (MTN) neurons innervate the stretch receptors of the jaw elevator muscles and periodontal ligament mechanoreceptors. Bruxism activates the MTN. We analyzed how MTN cells are structured, their anatomy and physiology, and the effects of their activation.

To induce and maintain sleep, gamma-aminobutyric acid (GABA), an inhibitor neurotransmitter, is released from the ventro-lateral preoptic area of the hypothalamus and acts on the ascending reticular activating system (ARAS) nuclei. The GABA neurotransmitter induces the entry of chlorine into cells, hyperpolarizing and inhibiting these. MTN cells, on the contrary, are depolarized by GABA, as their receptors are activated upon GABA binding. They “let out” chlorine and activate ARAS cells. MTN cells release glutamate, an excitatory neurotransmitter onto their target cells, in this case onto ARAS cells. During wakefulness, ARAS activation causes cerebral cortex activation; instead, during sleep (sleep bruxism), ARAS activation avoids an excessive reduction in ARAS neurotransmitters, including noradrenaline, dopamine, serotonin, acetylcholine and glutamate. These neurotransmitters, in addition to activating the cerebral cortex, modulate vital functions such as cardiac and respiratory functions. Polysomnography shows that sleep bruxism is always accompanied by cardiac and respiratory activation and, most importantly, by brain function activation. Bruxism is not a parafunction, and it functions to activate ARAS nuclei.

## 1. Introduction

In 2013, consensus was obtained on a definition of bruxism as repetitive masticatory muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible, and specified as either sleep bruxism or awake bruxism [1]. Bruxism directly involves the teeth and masticatory muscles; therefore, the trigeminal nerve, whose central nuclei include the mesencephalic trigeminal nucleus (MTN), the main sensory nucleus and the trigeminal spinal nucleus [2].

## 2. Methods

We performed a thorough search of the main search engines (PubMed; PubMed Central; Medline Plus; The Cochrane Library; Medscape; NLM Gateway; Google Scholar) regarding everything that is known about the mesencephalic trigeminal nerve.

## 3. Results

The mesencephalic trigeminal nerve (MTN) is not a nucleus but a ganglion and is the only intraneuraxial ganglion. The MTN is mostly

composed of large, glutamatergic, pseudounipolar cells [3], characterized by the presence of GABA-A receptors. These receptors depolarize upon the binding of gamma-aminobutyric acid (GABA), and they allow only chlorine ions to exit the cells [4, 5, 6], similar to prenatal GABAergic neurons [7, 8, 9, 10]. Normally, GABA increases chlorine ion conductance, which, upon entering the cell, makes the postsynaptic membrane potential more negative and thereby decrease the probability that an action potential will be induced.

The peripheral branches of MTN neurons innervate the stretch receptors of the jaw elevator muscles and periodontal ligament mechanoreceptors [11]. The central branches provide glutamatergic signals to the trigeminal motor nucleus (Mo5) [3]. They project upwards toward the orexinergic hypothalamic nuclei [12] and laterally toward the adjacent locus coeruleus (LC) nucleus (the main source of noradrenergic fibers), the reticular parvocellular area, the mesencephalic reticular formation, the dorsal raphe nucleus (DRN, the main source of serotonergic fibers), and to the latero-dorsal tegmental (LDT) nucleus [11, 13] (the main source of cholinergic fibers in the brainstem). The central branches of MTN neurons then descend into the latero-tegmental area, forming the Probst tract, finally terminating at the caudal trigeminal nucleus and up to the first segments of the spinal cord [14, 15].

\* Corresponding author.

E-mail address: [studioandrisani@virgilio.it](mailto:studioandrisani@virgilio.it) (A. Giovanni).

It should be noted that the efferent branch of these cells innervates only two structures: the chewing muscles and the periodontium. Therefore, MTN is activated with the opening and closing of the mouth and with dental contact, implying that the MTN is particularly active during bruxism. In addition, MTN nerve endings, afferent to the central nervous system, release only glutamate and therefore are excitatory. These MTN cells release glutamate to the ascending reticular activating system (ARAS) nuclei.

ARAS nuclear cells release neurotransmitters (NTs), including noradrenaline, dopamine, serotonin, acetylcholine, and glutamate, with a small proportion released directly into the cerebral cortex and exciting it, while the majority is released into the thalamus and basal forebrain. This, in turn, excites the cerebral cortex [16, 17, 18, 19, 20, 21]. Some afferent MTN fibers innervate the trigeminal motor nucleus (Mo5).

MTN pseudounipolar cells are equipped with prenatal GABA-A receptors that activate ARAS cells [15, 16, 17, 18, 19, 20] and are activated by GABA [4, 5, 6], which is released to induce and maintain sleep.

To induce and maintain sleep, the central nervous system inhibits ARAS nuclei through the hypothalamic ventro-lateral preoptic (VLPO) nucleus and other nuclei, such as the thalamic reticular nucleus and nucleus accumbens [22]. The neurons of these nuclei use inhibitor neurotransmitters such as GABA and galanin, and their connections are directed toward the ARAS nuclei neurons, particularly the orexinergic neurons of the lateral hypothalamus, the histaminergic neurons of the tubero-mammillary nucleus (TMN), the serotonergic neurons of the DRN, the noradrenergic neurons of the LC, and the cholinergic neurons of the basal forebrain (BFC), LDT, and pedunculo-pontine tegmentum (PPT). When hypothalamic GABA is released on ARAS nuclei neurons, their neurotransmitters, including serotonin, orexin, and noradrenaline, among others, are neither produced nor released [23, 24].

#### 4. Interpretation

GABA, released by the hypothalamic nucleus VLPO, activates the MTN which, in turn, can activate the ARAS nuclei. The activation of ARAS nuclei by MTN during sleep prevents an excessive reduction in the aforementioned ARAS neurotransmitters that, in addition to activating the cerebral cortex, also support cardiac and respiratory function during wakefulness and sleep. Therefore, MTN and sleep bruxism have an important protective role.

We can verify ARAS nuclear activation and its association with sleep bruxism experimentally. During polysomnography, sleep bruxism is identified through several means: by electromyography through rhythmic masticatory muscle activity (RMMA) that represents the polysomnographic manifestation of sleep bruxism [1]; with an electrocardiogram as the heart rate increases in association with sleep bruxism [25, 26]; through an increase in breathing rate [27]; and, most importantly, in the electroencephalogram, which shows an increase in cerebral cortex activity during sleep bruxism [28, 29, 30, 31].

#### 5. Therapies

Sleep bruxism cannot be eliminated because this would also eliminate GABA, and without GABA there is no sleep. Very little is known about the complex relationship between drugs and GABA release in the context of sleep; however, we cannot help but notice that some GABA agonist drugs (alcohol, phenethylamines (amphetamines and methylphenidate), heroin, anticonvulsants, and selective serotonin reuptake inhibitors) favor sleep bruxism while some GABA antagonists (clonidine, levodopa, clonazepam, gabapentin, hydroxyzine, and dopamine agonists) reduce it [32, 33].

#### 6. Conclusion

Bruxism stimulates ARAS nuclei, so it is not a parafunction. Its function is to activate the production of ARAS neurotransmitters that

stimulate the cerebral cortex, as confirmed by chewing studies [34, 35, 36, 37]. When bruxism no longer works properly (e.g., in elderly edentulous patients without dentures), individuals are at higher risk of developing dementia [38, 39, 40, 41, 42, 43, 44, 45].

#### Declarations

##### Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

##### Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

##### Data availability statement

Data included in article/supplementary material/referenced in article.

##### Declaration of interests statement

The authors declare no conflict of interest.

##### Additional information

No additional information is available for this paper.

#### References

- [1] F. Lobbezoo, J. Ahlberg, K.G. Raphael, et al., International consensus on the assessment of bruxism: report of a work in progress, *J. Oral Rehabil.* 45 (11) (2018 Nov) 837–844.
- [2] H. Gray, S. F.R., *Anatomy of the Human Body*, Lea & Febiger, Philadelphia, 1985 pg.886.
- [3] A. Espana, F. Clotman, One cut factors control development of the locus coeruleus and of the mesencephalic trigeminal nucleus, *Mol. Cell. Neurosci.* 50 (1) (2012 May) 93–102.
- [4] Y. Yokomizo, Y. Murai, E. Tanaka, et al., Excitatory GABAergic synaptic potentials in the mesencephalic trigeminal nucleus of adult rat in vitro, *Neurosci. Res.* 51 (4) (2005 Apr) 463–474.
- [5] A. Hayar, M.O. Poulter, K. Pelkey, et al., Mesencephalic trigeminal neuron responses to gamma-aminobutyric acid, *Brain Res.* 753 (1) (1997 Apr 4) 120–127.
- [6] H. Ishii, Y. Kang, Molecular basis underlying GABA(A) response in rat mesencephalic trigeminal neurons, *Neuroreport* 13 (17) (2002 Dec 3) 2265–2269.
- [7] Y. Ben-Ari, I. Khalilov, K.T. Kahle, et al., The GABA excitatory/inhibitory shift in brain maturation and neurological disorders, *Neuroscientist* 18 (5) (2012 Oct) 467–486.
- [8] Eric Herlenius, Hugo Lagercrantz, Development of neurotransmitter systems during critical periods, *Exp. Neurol.* 190 (Suppl 1) (2004 Nov) S8–21.
- [9] R. Miles, Neurobiology, A homeostatic switch, *Nature* 397 (6716) (1999 Jan 21) 215–216.
- [10] C. Rivera, J. Voipio, J.A. Payne, et al., The K<sup>+</sup>/Cl<sup>-</sup> co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation, *Nature* 397 (6716) (1999 Jan 21) 251–255.
- [11] A. Yoshida, M. Moritani, Y. Nagase, et al., Projection and synaptic connectivity of trigeminal mesencephalic nucleus neurons controlling jaw reflexes, *J. Oral Sci.* 59 (2) (2017) 177–182.
- [12] S. Yokoyama, K. Kinoshita, Y. Muroi, et al., The effects of bilateral lesions of the mesencephalic trigeminal sensory nucleus on nocturnal feeding and related behaviors in mice, *Life Sci.* 93 (18-19) (2013 Nov 4) 681–686.
- [13] J.T. Rokx, P.J. Jüch, J.D. van Willigen, Arrangement and connections of mesencephalic trigeminal neurons in the rat, *Acta Anat. (Basel)* 127 (1) (1986) 7–15.
- [14] N. Wang, P.J. May, Peripheral muscle targets and central projections of the mesencephalic trigeminal nucleus in macaque monkeys, *Anat. Rec. (Hoboken)* 291 (8) (2008 Aug) 974–987.
- [15] M.A. Pombal, R. Alvarez-Otero, M.C. Rodicio, et al., A tract-tracing study of the central projections of the mesencephalic nucleus of the trigeminal in the guppy (*Lebistes reticulatus*, teleostei), with some observations on the descending trigeminal tract, *Brain Res. Bull.* 42 (2) (1997) 111–118.
- [16] G. Moruzzi, H. Magoun, Brainstem reticular formation and activation of the EEG, *Electroencephalogr. Clin. Neurophysiol.* 1 (4) (1949) 455–473.
- [17] M. Steriade, R.W. McCarley, *Brainstem Control of Wakefulness and Sleep*, Springer, US, 1990.

- [18] J. Lu, T.C. Jhou, C.B. Saper, Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter, *J. Neurosci.* 26 (1) (2006) 193–202.
- [19] M.E. Carter, O. Yizhar, S. Chikahisa, et al., Tuning arousal with optogenetic modulation of locus coeruleus neurons, *Nat. Neurosci.* 13 (12) (2010) 1526–1533.
- [20] P. Fuller, D. Sherman, N.P. Pedersen, et al., Reassessment of the structural basis of the ascending arousal system, *J. Comp. Neurol.* 519 (5) (2011) 933–956.
- [21] M. Xu, S. Chung, S.Y. Zhang, et al., Basal forebrain circuit for sleep-wake control, *Nat. Neurosci.* 18 (11) (2015) 1641–1647.
- [22] P.H. Luppi, P. Fort, Neuroanatomical and neurochemical bases of vigilance states, *Handb. Exp. Pharmacol.* (2018 Feb 24) 35–58.
- [23] R. Szymusiak, D. McGinty, Hypothalamic regulation of sleep and arousal, *Ann. N. Y. Acad. Sci.* 1129 (2008) 275–286.
- [24] C.H.C. Leenaars, S.A. Savelyev, S. Van der Mierden, et al., Intracerebral adenosine during sleep deprivation: a meta-analysis and new experimental data, *J. Circadian Rhythms* 16 (2018 Oct 9) 11.
- [25] N. Huynh, T. Kato, P.H. Rompré, et al., Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity, *J. Sleep Res.* (2006 Sep).
- [26] G.J. Lavigne, N. Huynh, T. Kato, et al., Genesis of sleep bruxism: motor and autonomic-cardiac interactions, *Arch. Oral Biol.* 52 (4) (2007 Apr) 381–384.
- [27] S. Khoury, G.A. Rouleau, P.H. Rompré, et al., A significant increase in breathing amplitude precedes sleep bruxism, *Chest* 134 (2) (2008 Aug) 332–337.
- [28] F. Lobbezoo, M. Naeije, et al., Bruxism is mainly regulated centrally, not peripherally, *J. Oral Rehabil.* 28 (12) (2001 Dec) 1085–1091.
- [29] T. Kato, P. Rompré, J.Y. Montplaisir, et al., Sleep bruxism: an oromotor activity secondary to micro-arousal, *J. Dent. Res.* 80 (2001) 1940.
- [30] G.J. Lavigne, T. Kato, A. Kolta, et al., Neurobiological mechanisms involved in sleep bruxism, *Crit. Rev. Oral Biol. Med.* 14 (1) (2003) 30–46.
- [31] G.J. Lavigne, P.H. Rompré, G. Poirier, et al., Rhythmic masticatory muscle activity during sleep in humans, *J. Dent. Res.* 80 (2) (2001 Feb) 443–448.
- [32] Trotti Lynn Marie, C. Ong Jason, T Plante David, et al., Disease symptomatology and response to treatment in people with idiopathic hypersomnia: initial data from the Hypersomnia Foundation registry, *Sleep Med.* 75 (2020 Sep 2) 343–349.
- [33] Cees de Baat, Merel Verhoeff, Jari Ahlberg, et al., Medications and addictive substances potentially inducing or attenuating sleep bruxism and/or awake bruxism, *J. Oral Rehabil.* (2020 Jul 27).
- [34] Y. Hirano, M. Onozuka, Chewing and cognitive function, *Brain Nerve (Tokyo)* 66 (1) (2014) 25–32.
- [35] Y. Hirano, T. Obata, H. Takahashi, et al., Effects of chewing on cognitive processing speed, *Brain Cognit.* 81 (3) (2013) 376–381.
- [36] A. Smith, Effects of chewing gum on mood, learning, memory and performance of an intelligence test, *Nutr. Neurosci.* 12 (2) (2009) 81–88.
- [37] K. Morgan, A.J. Johnson, C. Miles, Chewing gum moderates the vigilance decrement, *Br. J. Psychol.* 105 (2) (2014) 214–225.
- [38] S. Mayor, Gum disease is an early sign of diabetes, and tooth loss is associated with risk of dementia, studies find, *BMJ* 356 (2017) j1225.
- [39] K. Takeuchi, T. Ohara, M. Furuta, T. Takeshita, Y. Shibata, et al., Tooth loss and risk of dementia in the community: the Hisayama study, *J. Am. Geriatr. Soc.* 65 (5) (2017) e95–e100.
- [40] P.P. Tonsekar, S.S. Jiang, G. Yue, Periodontal disease, tooth loss and dementia: is there a link? A systematic review, *Gerodontology* 34 (2) (2017) 151–163.
- [41] T. Shen, J. Lv, L. Wang, et al., Association between tooth loss and dementia among older people: a meta-analysis, *Int. J. Geriatr. Psychiatr.* 31 (8) (2016) 953–955.
- [42] D.A. Felton, Complete edentulism and comorbid diseases: an update, *Felton DA, J. Prosthodont.* 25 (1) (2016) 5–20.
- [43] J. Luo, B. Wu, Q. Zhao, et al., Association between tooth loss and cognitive function among 3063 Chinese older adults: a community-based study, *PLoS One* 10 (3) (2015), e0120986.
- [44] R. Stewart, U. Stenman, M. Hakeberg, et al., Associations between oral health and risk of dementia in a 37-year follow-up study: the prospective population study of women in Gothenburg, *J. Am. Geriatr. Soc.* 63 (1) (2015) 100–105.
- [45] J. Zhu, X. Li, F. Zhu, et al., Multiple tooth loss is associated with vascular cognitive impairment in subjects with acute ischemic stroke, *J. Periodontol. Res.* 50 (5) (2015) 683–688.