Neurobiology of bruxism: The impact of stress (Review)

IOANNIS A. PAVLOU[1], DEMETRIOS A. SPANDIDOS[2], VASSILIS ZOUMPOURLIS[3] and VERONICA K. PAPAKOSTA[4]

[1]Iasis Dental (Private Practice), 12241 Athens; [2]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion; [3]Biomedical Applications Unit, Institute of Chemical Biology, National Hellenic Research Foundation, 11635 Athens; [4]Department of Oral and Maxillofacial Surgery, University Hospital Attikon, 12462 Athens, Greece

Received October 17, 2023; Accepted January 30, 2024

DOI: 10.3892/br.2024.1747

Abstract. Bruxism is a non-functional involuntary muscle activity that affects more than one-third of the population at some point in their lives. A number of factors have been found to be related to the etiopathogenesis of bruxism; therefore, the condition is considered multifactorial. The most commonly accepted factor is stress. Stress has long been considered to increase muscle tone and to reduce the pain threshold. Current evidence indicates that exposure to chronic stress, distress and allostatic load ignite neurological degeneration and the attenuation of critical neuronal pathways that are highly implicated in the orofacial involuntary muscle activity. The present review discusses the negative effects that chronic stress exerts on certain parts of the central nervous system and the mechanisms through which these changes are involved in the etiopathogenesis of bruxism. The extent of these morphological and functional changes on nerves and neuronal tracts provides valuable insight into the obstacles that need to be overcome in order to achieve successful treatment. Additionally, particular emphasis is given on the effects of bruxism on the central nervous system, particularly the activation of the hypothalamic-pituitary-adrenal axis, as this subsequently induces an increase in circulating corticosterone levels, also evidenced by increased levels of salivary cortisol, thereby transforming bruxism into a self-reinforcing loop.

Correspondence to: Dr Ioannis A. Pavlou, Iasis Dental (Private Practice), 7 Stefanou Sarafi Street, 12241 Athens, Greece
E-mail: iasisdental@gmail.com

Abbreviations: Ache, acetylcholinesterase; ACTH, adrenocorticotropic hormone; BLA, basolateral amygdala; CK, creatinine kinase; CRH, corticotropin-releasing hormone; DA, dopamine or dopaminergic; GABA, gamma-aminobutyric acid; HPA axis, hypothalamic-pituitary-adrenal axis; LC, locus coeruleus; Me5, mesencephalic trigeminal nucleus; N.Acc, nucleus accumbens; NE, norepinephrine; OX, orexine; PAG, periaqueductal gray; PVN, paraventricular nucleus; RF, reticular formation; TMD, temporomandibular disorder; TMN, tuberomammillary nucleus; VP, ventral pallidum; vSub, ventral subiculum (of hippocampus); VTA, ventral tegmental area

Key words: chronic stress, HPA axis, hippocampus, neurodegeneration

Contents

1. Introduction

Bruxism is defined as a repetitive jaw muscle activity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible (1-3); however, it is not regarded as a movement disorder or a sleep disorder in otherwise healthy individuals (4). Bruxism is considered a very common condition, being present in 60-70% of the population; however, only 1 in 4 individuals with associated symptoms are aware of the condition (5). Based on the time of occurrence (circadian manifestations), two types of bruxism have been described thus far: i) Sleep bruxism, which is characterized by rhythmic masticatory muscle activity and occasional grinding; and ii) awake bruxism, characterized only by a clenching or bracing-type activity (1,6). Numerous researchers support a different etiology among the two types of bruxism, although no consensus has yet been reached regarding the mechanism. In a previous systematic review by Manfredini *et al* (7), it was reported that the prevalence of awake bruxism ranged from 22 to 31%, whereas the prevalence of sleep bruxism was 12,8%. Additionally, the condition appears to be more prevalent among females as compared to males, at a ratio of 5:1 (8,9).

A notable degree of controversy has surrounded the possible causes of bruxism over the years. Although the distinction between sleep and awake bruxism shows the time of occurrence, the actual difference between these two manifestations relies on the etiology. The definition of the condition based on etiology may be peripheral, due to peripheral reasons, such as

occlusion, trauma, peripheral fiber neuropathy, or central, due to neurotransmitter perturbations and/or neuronal pathway malfunction (10). Nonetheless, according to a number of epidemiological studies, the majority of bruxists fall into the category of the combined type (11), and this further complicates the differentiation; the most widely acknowledged factors involved in the etiopathogenesis of bruxism are emotional disturbances and stress, whereas more recent evidence also pinpoints towards genetic predisposition (12-15). In particular, when the patient experiences increased levels of emotional stress, this could lead to an increase in head and neck muscle tonicity, although it could also lead to an increase in the level of non-functional muscle activity, such as bruxism or tooth clenching (16). Furthermore, the sympathetic activity or tone may also be influenced by emotional stress (16). It can be reasoned that prolonged sympathetic nervous system activity has a marked impact on certain types of tissue, such as the muscle (16). In this regard, increased sympathetic activity, by increasing muscle tone and subsequently by inducing a painful muscle condition, may constitute an etiological factor that can influence temporomandibular disorder (TMD) symptoms (16,17).

The most widely accepted factor in the etiopathogenesis of bruxism is stress, with recent evidence highlighting that exposure to chronic stress may affect the attenuation of neuronal pathways involved in the orofacial involuntary muscle activity. The present review discusses the negative effects of exposure to chronic stress on the central nervous system and in the etiopathogenesis of bruxism. Particular emphasis is given on the effect of bruxism on the activation of the hypothalamic-pituitary-adrenal axis (HPA) axis, as this subsequently induces an increase in circulating corticosterone levels, also evidenced by increased levels of salivary cortisol, thereby transforming bruxism into a self-reinforcing loop. Overall, the present review aimed to provide valuable insight into the neurological sequelae of chronic stress exposure, and on the mechanisms through which these sequelae may be overcome in order to improve or alleviate bruxism and related symptoms.

2. Effect of stress on the genesis of bruxism

Stress is the most commonly accepted factor involved in the pathogenesis of bruxism. To be more precise, we must refer to *Distress* and *Allostatic load*. According to the American Psychological Association and the Dictionary of Psychology, *Distress* is defined as '*...the negative stress response, often involving negative affect and physiological reactivity: a type of stress that results from being overwhelmed by demands, losses, or perceived threats. It has a detrimental effect by generating physical and psychological maladaptation and posing serious health risks for individuals*; in addition, *Allostatic load* is described as '*the cumulative burden of chronic stress and life events. It involves the interaction of different physiological systems at varying degrees of activity. When environmental challenges exceed the individual ability to cope, then allostatic overload ensues*' (18). Animals under experimental stress conditions present with increased masseter activity (19) in humans, diurnal tooth clenching, bruxism and nail-biting seem to appear most frequently in individuals who experience panic (20).

When humans are under conditions of stress, the HPA axis, the main neuroendocrine response to stress, is activated. Through the hypothalamic [corticotropin-releasing hormone (CRH)]-pituitary [adrenocorticotropic hormone (ACTH)]-adrenal route, glucocorticoids (GCs) are released into the bloodstream. Nonetheless, CRH activates one more neuronal pathway: That of the sympathetic-adreno-medullary axis, which appears to take place via the induction of locus coeruleus (LC), which in turn causes the activation of the sympathetic system. The latter leads to the release of norepinephrine (NE), which promotes physiological responses to stress, thereby counteracting the activation of the HPA axis. The LC-NE system is a potent modulator of the ventral subiculum (of hippocampus) (vSub) neuronal activity, which may also contribute to stress adaptation. The vSub innervates several limbic structures, suggesting an upstream influence on limbic stress integration (21). An LC projection is also received by the amygdala, namely the basolateral nucleus (BLA), which is similarly stimulated under stress (22).

Implication of stress in orofacial musculature modulation. The normal hormonal response to stress is altered by ventral tegmental area (VTA) lesions, which implies that the dopamine system has an impact on the HPA axis (23). Equivalent, yet opposing modulatory effects on VTA dopaminergic neuron firing are produced by the vSub and the BLA, both of which constitute neurons that are normally being held at a hyperpolarized inactive state (24). It is also known that the neuroanatomy of masticatory modulation is a two-neuron chain, where serotonergic neurons from the raphe nucleus project to the VTA and synapse with dopaminergic neurons. Central bruxism can occur in two polar conditions: In extreme hyperdopaminergic situations, such as the ones induced by amphetamines and levodopa (L-dopa) and in the presence of cholinergic hypofunction, as well as in hypodopaminergic states, which appear to take place in cases of extrapyramidal system dysfunction (10).

It has also been shown that certain neurological conditions (Parkinson's or Huntington's disease) (25-28), or certain medications (such as selective serotonin reuptake inhibitors) (27-29) that alter the function of the serotonin 5-hydroxytryptamine (5-HT) receptors, can cause secondary bruxism. A genetic polymorphism of the serotonin-2A receptor gene that causes structural alterations and changes in the expression of 5-HT receptors, is highly associated with bruxism (14,15). The role of peripheral 5-HT2A receptors in the mediation of orofacial nociception has been well documented (30,31). Although it appears that a malfunction of the 5-HT2 receptors is involved in the pathogenesis of bruxism, there is the paradox of 5-HT1 agonists being used as a drug of choice in bruxism. The explanation for this discrepancy is considered to rely on the VTA, where synapsis between presynaptic serotonergic 5-HT neurons and dopaminergic neurons occurs. Any alterations on or between 5-HT1 and 5-HT2 receptors at the presynaptic level, will have a prominent negative effect on the mesocortical dopaminergic tract (10), which has essential functions in controlling involuntary muscle movements (Fig. 1).

Stress is also known to cause numerical area-dependent changes on 5-HT receptors. Specifically, stress invokes a reduction in 5-HT1A receptors in the hippocampus; however,

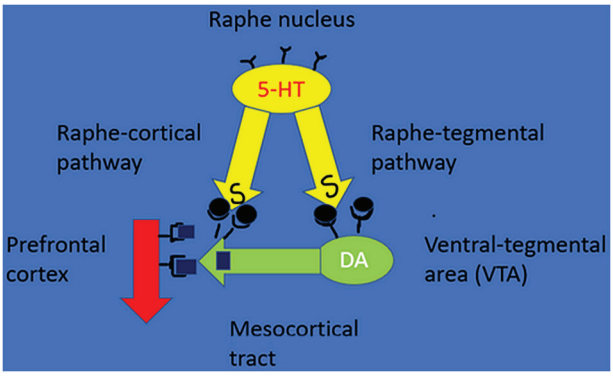

Figure 1. Serotinergic 5-HT neurons from the raphe nucleus synapse in the ventral tegmental area with mesocortical dopaminergic neurons that innervate up to the prefrontal cortex. Any changes at presynaptic or postsynaptic level will strongly affect the mesocortical dopaminergic tract. Serotonin is depicted in black dots, whereas dopamine is represented by blue squares. DA, dopamine; 5-HT, 5-hydroxytriptamine; S, serotonin.

at the same time, it causes an increase in cortical 5-HT1A receptors (32). On the other hand, the 5-HT2A receptors, which can be found in motor, sensory and spinal trigeminal nuclei, among other areas, appear to be unaffected (33). İnan *et al* (34) concluded that this is a case of the abnormally reduced inhibition of trigeminal motoneurons to the masseter muscle and not to the reticulobulbar pathways in bruxers. In addition, trigeminal nuclei lack GC and mineralocorticoid receptors, and are therefore unlikely to be affected by stress, at least not directly.

Mechanisms through which stress affects the mesocortical dopaminergic pathway. The activation of the vSub-ventral pallidum (VP)-nucleus accumbens (N.Acc) normally occurs under acute, mild and predictable stressors and leads to hyperdopaminergic states (35,36). Conversely, in chronic mild stressors, this pathway is attenuated, and the BLA-VP pathway is activated. This results in a decrease in the dopaminergic neuronal population in the medial and central tracks of VTA (37). The subsequent dopamine depletion in the caudate nucleus and N.Acc is associated with decreased dopamine functioning in the mesolimbic pathway, where dopamine normally acts as an inhibitor to spontaneous movement (38). This observation has been supported by the recent findings of Ueno *et al* (39), where the motor representation of rhythmic jaw movement of the amygdala was assessed in an animal model. The authors concluded that the ventral part of the amygdala (medial, basal and cortical) is highly involved in the induction of rhythmic jaw movement and that the role of limbic system in the genesis of bruxism warrants further investigation (39) (Fig. 2).

Normally, gamma-aminobutyric acid (GABA)-ergic neurotransmission inhibits the amygdala from producing inappropriate emotional and behavioral reactions (40). GABA is crucial in maintaining a balance between neuronal activation and inhibition (41). BLA entails mainly glutamatergic and considerably less GABAergic neurons; however, even this small number of GABAergic neurons is sufficient to induce an inhibitory effect on principal glutamatergic neurons (42). It has already been documented that chronic stress invokes the loss of the tonic inhibition of the amygdala via impaired GABA gating (43); such a disruption can lead to hyperexcitability, increased anxiety and depression (42).

Notably, susceptibility to social stress appears to be induced by inhibiting the mesocortical system, a situation that is similarly observed in both bruxists and patients with TMD who are more susceptible to new forms of stress (44). Males and females react differently to prolonged stress, as the dopaminergic system displays sex-specific morphological and molecular alterations. As a result, stress causes a redesign of the dopaminergic mesocortical and mesolimbic circuits, as well as a sharp decrease in dopaminergic inputs from the VTA (44). These molecular changes influencing intracellular signaling in dopaminergic neurons and their target brain regions are linked to morphological changes in dopaminergic circuits brought on by chronic stress (45,46).

There is substantial evidence to suggest that alterations in the mesolimbic dopaminergic neurons are actively implicated in both neuropathic and chronic pain (47). The reduced neuronal activity of VTA dopamine neurons and the reduced dopaminergic activation of N.Acc. in response to painful stimuli have both been noted in chronic and neuropathic pain (48,49). The lack of regulation of dopamine D2 receptor expressing indirect pathway output neurons, which may promote hypersensitivity to pain (50) and increased impulsivity (51), has been attributed to the lower dopamine levels in the N.Acc. Watanabe *et al* (47) demonstrated that the stimulation of VTA-dopamine neurons and the stimulation of N.Acc. suppressed the allodynic effect of neuropathic pain. These neuronal changes in VTA-dopamine neurons and subsequently in N.Acc. have a prominent effect on the mesencephalic trigeminal nucleus (Me5).

Implication of the mesocortical dopaminergic pathway in bruxism. Animal electrophysiological research has demonstrated that chronic restrained stress causes an enhanced excitability of Me5 neurons (52). As a result of this excitability, an increase in glutamatergic neurotransmission from Me5 to the trigeminal motor nucleus (Mo5) has been observed by performing western blot analysis of vesicular glutamate transporter 1 (VGLUT1) protein overexpression in the Mo5, resulting in increased overactivity of the masseter muscle, as verified via the evaluation of acetylcholinesterase (AchE) and creatinine kinase (CK)-MM levels (52). AChE dictates the rapid breakdown of acetylcholine, which is essential for skeletal muscle contraction (53). The most prevalent CK isoenzyme found in skeletal muscle is CK-MM. Increased levels indicate muscle overactivity and subsequent muscle fatigue and pain (54). In an attempt to analyze the neuroplasticity changes caused by bruxism or related to bruxism, Boscato *et al* (55) came to the following conclusion: '*Bruxism seems, indeed, to be connected with significant abnormalities in the brain circuits related to the control of the jaw-closing muscles*'. This notion is further supported by data regarding another clinical entity, the burning mouth syndrome (BMS). BMS is a chronic orofacial condition characterized by a burning or numbing sensation that recurs for >2 h per day, for >50% of the days, for >3 months, without any evident causative lesions (56). BMS is considered a neuropathic condition and can result from either peripheral small fiber neuropathy of the trigeminal nerve, or a central type due to hypodopaminergic neuron activity in

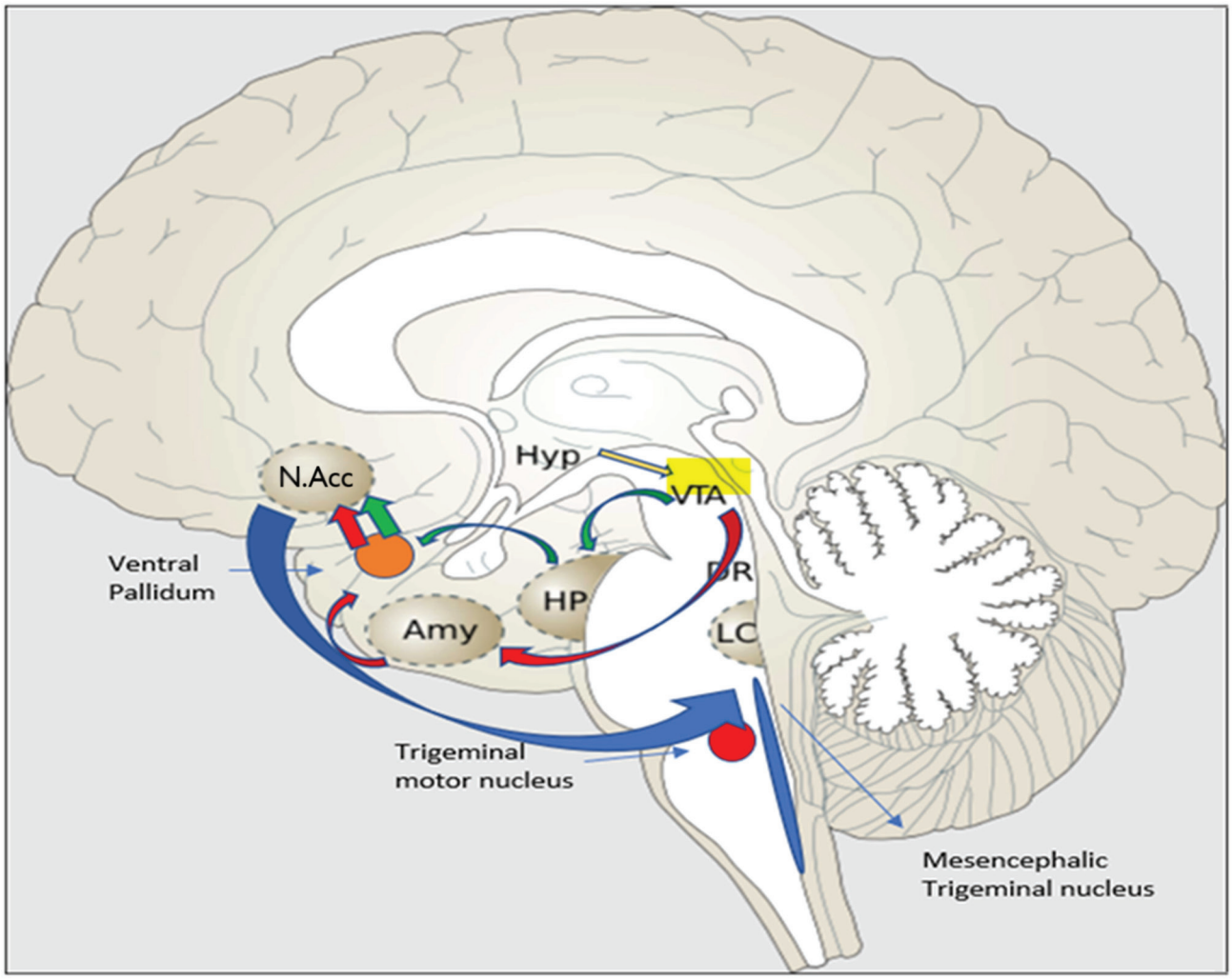

Figure 2. Serotinergic 5-HT neurons from the raphe nucleus synapse in the VTA with dopaminergic neurons, which control spontaneous muscle movements. These tracts follow either the vSub (hippocampus) route or the BLA route, depending on the stressors. In acute and mild stressors, the vSub-VP-N.Acc is activated, while in chronic and severe stressors, the aforementioned tract becomes destabilized and the BLA-VP-N.Acc tract is activated. 5-HT, 5-hydroxytriptamine; vSub, ventral subiculum; VTA, ventral tegmental area; VP, ventral pallidum; N.Acc, nucleus accumbens; BLA, basolateral amygdala; Amy, amygdala; Hyp, hypothalamus; HP, hippocampus; DR, dorsal raphe nucleus; LC, locus coeruleus.

the basal ganglia or a nerve system pathology including the trigeminal (57). A noteworthy fact about this condition is that 72.7% of patients reporting symptoms of BMS exhibit parafunctional habits; for example, 77% present with wear facets, while 65.9% exhibit signs or symptoms of TMD according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (58). In this context, it has been hypothesized that BMS and parafunctional habits (bruxism) may share common pathways. Lauria *et al* (59) demonstrated that such a neuropathy in the nigrostriatal dysfunction leads to a loss of inhibition of the trigeminal nerve, thereby resulting in sensory and motor hyperfunction and mastication muscle hyperactivity. Patients with BMS present with abnormal reflex responses in neurological tests (blink reflex), similar to what is observed in bruxists in masseter inhibitory reflex (60).

The activation of the N.Acc. occurs either via the vSub-VP pathway or via the BLA-VP pathway. However, acute and chronic stress exposure, and subsequently an increase in circulating corticosterone levels, are also known to diminish progenitor cell proliferation, inhibit neuronal differentiation and suppress cell survival in the hippocampus dentate gyrus; all of these actions affect hippocampal neurogenesis (61-64) and may result in cognitive deficiencies that are associated with the hippocampus (65-67). The ability of the hippocampus to negatively modulate the HPA axis is dependent on the neurogenesis of the hippocampal dentate gyrus (68). Therefore, the activation of N.Acc and subsequently of the Me5 occurs via the amygdala-ventral pallidum pathway. There have been reports of direct projections from the central nucleus of the amygdala to the Me5, which are crucial for the perception and control of negative emotions (69). This type of projection has been connected to stronger biting attacks during hunting in animal studies and has recently been identified in humans as well (70,71).

3. Mesencephalic trigeminal nucleus

Current evidence highlights that bruxism can also act as a stressor via the activation of the Me5. The Me5 consists of a band of cells that run directly adjacent to the periaqueductal

gray (PAG) and extend from the boundary between the pons Varolii and the midbrain to the superior colliculus (upper boundary of the midbrain) (52). The inferior border of the Me5 lies rostral to the motor trigeminal nucleus and is surrounded by reticular formation (RF) (72).

The peripheral branches mainly innervate mechano-receptors in the periodontal ligament and the elevator muscles of the mandible. They are sensitive to jaw elevator muscle movement, and may be activated by even the lightest pressure (1N and 4N in the anterior and the posterior teeth, respectively) (73-75), and even in the complete absence of stimuli (76). The central branches of the Me5 are glutamatergic, the majority projecting to Mo5 (77), but also to the reticular parvocellular area and the dorsolateral midbrain RF, i.e., both to the dorsal raphe nucleus (DRN) and the laterodorsal tegmental nucleus (LDT). The midbrain RF nerve cells, in particular those of the DRN and LDT, form part of the ascending reticular activation system (ARAS) nuclei which, along with certain branches of the Me5, send specific projections to the entire cortex and the nuclei of hypothalamic orexinergic (78,79). Each time the upper and lower teeth occlude or the elevator muscles move, the Me5 is activated, and this in turn activates the ARAS nuclei, and in particular orexine (OX). The activation of both Me5 and ARAS nuclei is proportional to the pressure exerted on the teeth and the muscles (80).

OX plays a key role both in the pathogenesis of headaches, as well as in fostering and maintaining vigilance: Individuals with OX deficiency often present with narcolepsy (81-84). Orexinergic neurons are connected with every node that is involved in the sleep-awake cycle (81). The cerebral cortex is both directly and indirectly excited by the orexinergic nuclei. OX the activates LDT, pedunculopontine tegmental nucleus, dorsal raphe, LC, VTA, PAG and tuberomammillary nucleus (TMN). Apart from the hypothalamic connections, OX cells send projections to the forebrain, cerebral cortex, hippocampus, amygdala and TMN (82). Furthermore, OX stimulates the release of GCs, autonomous functions, behavior, appetite, metabolic rate and gastric secretion (83-85). Therefore, when teeth come into contact and muscles contract through the Me5 and ARAS nuclei, the activation of the hypothalamus, forebrain and cerebral cortex occurs. This is supported by evidence that chewing improves cognitive performance and spatial memory, while tooth loss may lead to dementia (86,87). The observation that the hypothalamic activation follows this path and not the other way around is in agreement with the study by Cruccu *et al* (88), who produced masseter motor-evoked potentials of normal latency and amplitude in patients with bilateral and unilateral pain. They concluded that cerebral hyperactivity could not be the cause of discomfort and masticatory system dysfunction in these patients, based on the absence of facilitation in their reactions (88) (Fig. 3).

During sleep, the central nervous system is under the influence of the hypothalamic GABA. The only structure that is insensitive to GABA is the Me5, due to a lack of dendrites. ARAS nuclei are sensitive to GABA; thus, during sleep, they can only be activated through the Me5 (80). In addition, it has long been known that sleep is divided into rapid eye movement (REM) and non-REM (NREM, with NREM being characterized by the presence of the cyclic alternating pattern, where an individual moves from the arousal (A-phase) to the resting (B-phase) phase and vice versa. Arousals occur in every individual to maintain a state of alertness and to prevent the individual from falling into deep sleep for long periods of time (84). It has also been demonstrated that the A-phase has three different subtypes, two of which, namely A2 and A3, have a high prevalence in bruxists (81). In polysomnographic experiments conducted in a protected environment where there was a lack of external stimuli to initiate an arousal, the only stimuli observed were of internal origin and appeared to have occurred via the Me5 and ARAS nuclei (81).

By contrast, Me5 receives projections from the N.Acc which, as aforementioned, is an area of ventral striatum accepting excitatory glutamatergic inputs from cortical and limbic regions, including the hippocampus and the basolateral amygdala, and returns projections to both pallidal and mesencephalic motor effector sites; for this reason, it is considered a 'limbic-motor interface' (89). N.Acc receives dopaminergic inputs from the VTA, an area that is highly involved in the pathogenesis of bruxism, as aforementioned in the present review. These inputs are further modulated by inputs from either the hippocampus (vSub)-pallidal (VP) or the BLA-VP pathways, both of which are implicated in the association of stress with bruxism (90).

4. HPA axis and lateral habenula

Upon arrival of the signal to the hypothalamus, activation follows two neuronal pathways: The activation of the HPA axis and activation of the thalamus, particularly of the lateral habenula (LHb). Animal studies have identified a possible link between masticatory dysfunction and the activity of the HPA axis (61,62,91). CRH and arginine vasopressin (AVP) are secreted by the activated hypothalamic paraventricular nucleus (PVN) neurons into the pituitary portal system and subsequently induce the secretion of ACTH; circulating ACTH then activates the synthesis and secretion of GCs from the adrenal cortex. Experimentally induced occlusal disharmony in animals has resulted in increased circulating and urine corticosterone levels that persist for weeks (61,65,91-97). This disharmony appears to be in the form of bite-raising or tooth loss (98-100). In a previous systematic review and meta-analysis by Fritzen *et al* (101), higher levels of salivary cortisol were observed in adult patients with bruxism, but not in children, whereas no associations were made with bruxism or stress or anxiety.

The increased circulating levels of corticosterone appear to have notable consequences. Initially, they correlate with strong circadian rhythms, with peak levels occurring during the activation period (102), and with increased muscle tone (103-105). According to some researchers, the activation threshold for an episode of bruxism is reached when the muscle tone reaches 10% (106) or 20% (107-109) of the maximum voluntary contraction.

The hyperactivity of the HPA axis can cause an individual to be more sensitive and susceptible to novel stress. Experiments in mice where occlusal disharmony is caused by bite-raising procedures, have demonstrated shown that, apart from the increase in CRH and AVP in PVN due to bite-raising, exposure to novel stress further reinforces CRH-mRNA expression in PVN (110,111). Additionally, it has been noted that TMD

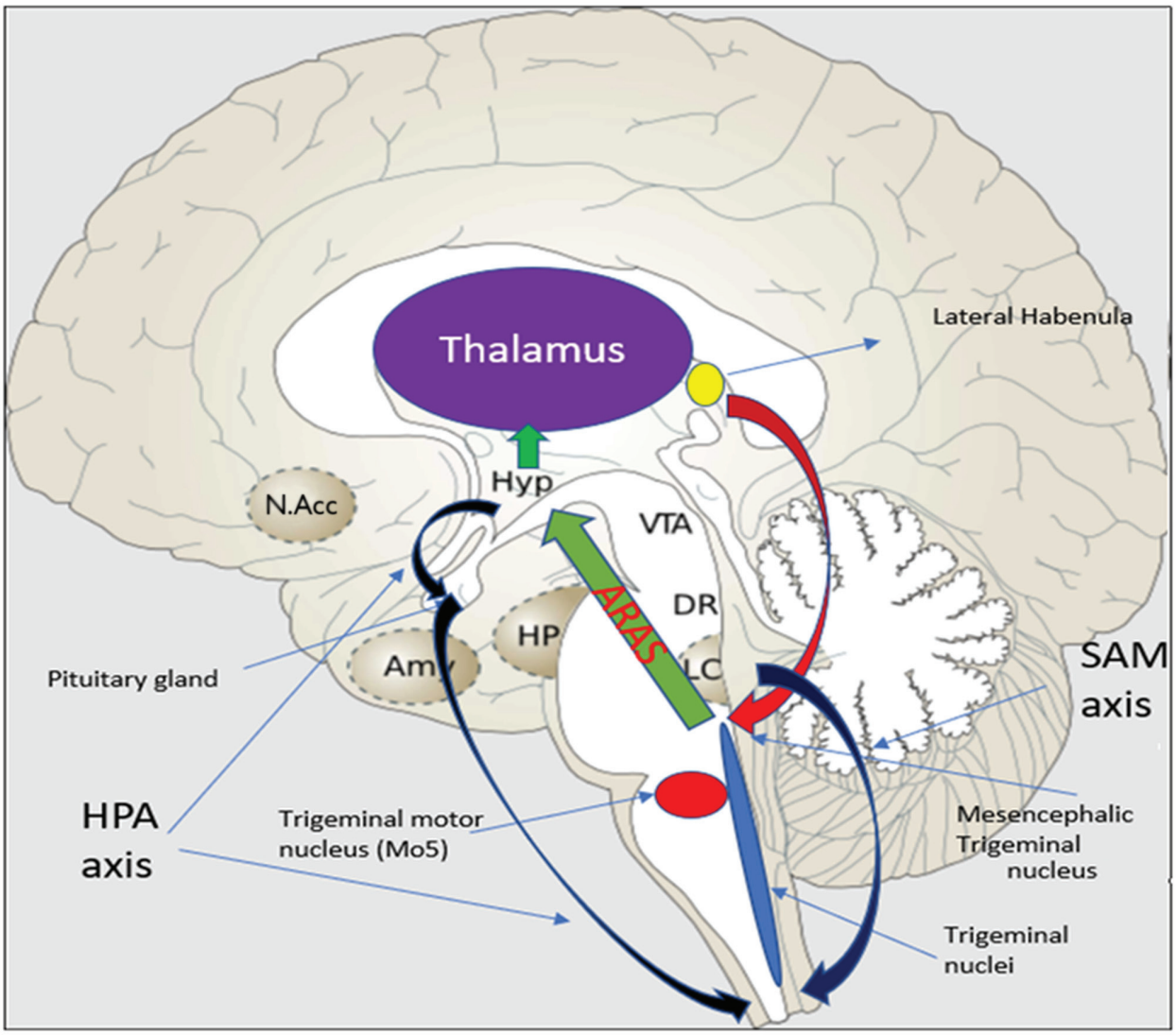

Figure 3. Activation of the mesencephalic trigeminal nucleus, via the ascending reticular activating system, leads to activation of the hypothalamus and the HPA axis. The activation of pituitary gland and the release of corticotropin-releasing hormone will lead to the activation of the LC and the SAM axis. HPA axis, hypothalamus-pituitary-adrenal axis; SAM, sympathetic-adreno-medullary; LC, locus coeruleus; N.Acc, nucleus accumbens; Amy, amygdala; Hyp, hypothalamus; HP, hippocampus; DR, dorsal raphe nucleus; VTA, ventral tegmental area.

sufferers frequently exhibit higher levels of anxiety and/or depression compared to asymptomatic control subjects (112), whereas TMD symptoms appear more commonly in individuals who are under stress (113).

Neuroimaging studies are beginning to provide evidence that masticatory dysfunction may result in hippocampus-dependent cognitive impairment (114,115). According to a growing body of research in animals, spatial memory and learning abilities are impaired by masticatory dysfunction brought on by tooth extraction or occlusal disharmony (61,62,91,94,116-122). Additionally, neurons of the hippocampus, dendritic spines, post-synaptic density, as well as the release of hippocampal acetylcholine, acetyltransferase and choline acetyltransferase activity, have all been identified by morphological analyses to be significantly decreased in toothless or bite-raised rodents (63,64,66,93,94,116,123-125). Notably, HPA hyperactivity and the inhibitory control of corticosterone have been shown to result in changes in the 5-HT receptors of the hippocampus, such as those observed in suicidal brains (32,126).

Recent evidence also highlights the importance of one more neuromuscular pathway, that of the LHb, which constitutes part of the epithalamus and is activated by the lateral hypothalamus, in addition to other areas of the brain (127,128). The habenula consists of two small nuclei located above the posterior end of the thalamus and is divided into medial habenula and LHb (113). The latter regulates the monoaminergic systems, dopamine and serotonin (129). Liu *et al* (113) demonstrated that an occlusal disharmony, such as a crossbite can stimulate the LHb. In addition, a direct one-way projection has been shown to stretch from the LHb to the Me5, as evidenced by using anterograde and retrograde track tracing (130). The LHb is additionally associated with a number of depressive symptoms (127,128,131) and sleep issues (111) and can be triggered by a number of stressors and unpleasant or aversive stimuli (132). Notably, this direct projection of the LHb to the Me5 is inhibitory and causes motor suppression; however, in cases of chronic pain, this loop of homeostatic inhibition by LHb appears to be disrupted (127,128). This motor

suppression can also occur indirectly through the activation of the medulla oblongata, which mediates the trigeminocardiac reflex (TCR). The TCR is induced in situations characterized by overactivation of the sympathetic system and results in the downregulation of the sympathetic system and the upregulation of the parasympathetic system (133). This will subsequently cause bradycardia, bradypnea and in some cases, apnea.

Similar neurodegenerative findings have been reported in sleep bruxists. Keskinruzgar *et al* (134) demonstrated that there was a decrease in retinal nerve fiber layer axon thickness, inferior parietal lobe dendrite and granule cell layer (soma) volume of the retinal ganglion cells in patients with sleep bruxism as compared to the controls, when optical coherence tomography measurements were used, suggesting retinal neuro-degeneration (135). Kalenderoglu *et al* (136) reported similar results in patients with major depression. The retina is regarded as a continuation of the brain, therefore any changes within the brain are also expected to take place in the retina. Another even more notable finding in the study by Keskinruzgar *et al* (134) is that choroidal thickness is changed in patients with sleep bruxism. The transport of nutrients and oxygen to the retina is carried out via the choroid, one of the most critical sites of vascularization.

5. Conclusion and future perspectives

Overall, the current review has highlighted the role of stress both as a precipitating and an initiating factor in the genesis of bruxism. Based on clinical evidence, it has been demonstrated that chronic stress can degenerate the hippocampus and destabilize the mesocortical dopaminergic pathway, which is responsible for the control of involuntary muscle movements. In this manner, it promotes the activation of the basolateral amygdala, which can in turn cause rhythmic jaw movement. If one considers that any malfunction at any point of the VTA-mesocortical-vSub-VP-N.Acc-Me5 pathway can cause bruxism, it is only logical to assume that this may provide an explanation as to why there is no specific medication that confers universal and consistently positive results; at the same time, the certainty of evidence produced by the majority of studies has been calculated in the range between very low and moderate (137,138). Similarly, the existence of neurological degeneration may constitute the reason why cognitive behavioral therapy is not successful as a bruxism management option, since it cannot reverse these neurological disturbances, at least not sooner than 6 months from the initiation of treatment (137). As an initiating factor, stress increases the muscle tone and when this increase rises to 10-20%, it may cause a bruxism event, in addition to reducing the pain threshold. On the other hand, a sudden alteration in occlusion, an occlusal instability which cannot be tolerated, as well as parafunctional activities, could generate stress which is demonstrated as increased levels of circulating corticosterone. In other words, bruxism appears as a self-sustained vicious circle. The present review suggests that stress management should be addressed as part of any treatment plan, as a maintenance program, irrespectively of the peripheral or central origin of bruxism; this does not mean that the possibility of a sudden change in peripheral sensory input should be underestimated, as it may be of utmost importance in the establishment and perpetuation of bruxism. Further studies are required in order to identify a medication, agent or supplement that has minimal or no adverse effects, and which is able to counteract the sequelae of chronic stress exposure, to re-activate the mesocortical-vSub pathway and to attenuate the BLA-VP-N. Acc pathway, which induces rhythmic jaw muscle activity.

Acknowledgements

This article is a part of and constitutes a (partial) requirement for the fellowship program on temporomandibular joint disorders (FTMJF) of the TMJ Foundation, TMJ Consultancy Services, Bhopal (Madhya Pradesh), India and DARSN Academy for Maxillofacial Education and Research, DAMER, India.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

IAP was involved in the conceptualization of the study. IAP and VKP were involved in the writing and preparation of the original draft. VKP, VZ and DAS were involved in the reviewing and editing of the manuscript. IAP and VKP were involved in the conceptualization of the topic and manuscript. VZ and VKP supervised the study. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

References

1. Commisso MS, Martinez-Reina J and Mayo J: A study of the temporomandibular joint during bruxism. Int J Oral Sci 6: 116-123, 2014.
2. Lobbezoo F, Ahlberg J, Glaros AG, Kato T, Koyano K, Lavigne GJ, de Leeuw R, Manfredini D, Svensson P and Winocur E: Bruxism defined and graded: An international consensus. J Oral Rehabil 40: 2-4, 2013.
3. K L: How sleep bruxism and tension headaches affect the masseter inhibitory reflex. J Sleep Disor Treat Care 6, 2017.
4. Lobbezoo F, Ahlberg J, Raphael KG, Glaros AG, Kato T, Santiago V, Winocur E, De Laat A, De Leeuw R, Koyano K, *et al*: International consensus on the assessment of bruxism: Report of a work in progress. J Oral Rehabil 45: 837-844, 2018.

5. Simoes WA: Occlusal plane: A clinical evaluation. J Clin Pediatr Dent 19: 75-81, 1995.
6. Lavigne GJ, Huynh N, Kato T, Okura K, Adachi K, Yao D and Sessle B: Genesis of sleep bruxism: Motor and autonomic-cardiac interactions. Arch Oral Biol 52: 381-384, 2007.
7. Manfredini D, Winocur E, Guarda-Nardini L, Paesani D and Lobbezoo F: Epidemiology of bruxism in adults: A systematic review of the literature. J Orofac Pain 27: 99-110, 2013.
8. Manfredini D, Piccotti F, Ferronato G and Guarda-Nardini L: Age peaks of different RDC/TMD diagnoses in a patient population. J Dent 38: 392-399, 2010.
9. Chisnoiu AM, Buduru S, Lascu L, Vesa SC, Picos AM, Pascu L and Chisnoiu R: Influence of occlusal characteristics on temporomandibular joint disorder development-a cross-sectional study. Hum Vet Med 7: 197-201, 2015.
10. Bostwick JM and Jaffee MS: Buspirone as an antidote to SSRI-induced bruxism in 4 cases. J Clin Psychiatry 60: 857-860, 1999.
11. Bayar GR, Tutuncu R and Acikel C: Psychopathological profile of patients with different forms of bruxism. Clin Oral Investig 16: 305-311, 2012.
12. Segall SK, Maixner W, Belfer I, Wiltshire T, Seltzer Z and Diatchenko L: Janus molecule I: Dichotomous effects of COMT in neuropathic vs nociceptive pain modalities. CNS Neurol Disord Drug Targets 11: 222-235, 2012.
13. Smith SB, Maixner DW, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade GD, Bair E, Gibson DG, *et al*: Potential genetic risk factors for chronic TMD: Genetic associations from the OPPERA case control study. J Pain 12 (11 Suppl): T92-T101, 2011.
14. Oporto GH V, Bornhardt T, Iturriaga V and Salazar LA: Genetic polymorphisms in the serotonergic system are associated with circadian manifestations of bruxism. J Oral Rehabil 43: 805-812, 2016.
15. Cruz-Fierro N, Martinez-Fierro M, Cerda-Flores RM, Gómez-Govea MA, Delgado-Enciso I, Martínez-De-Villarreal LE, González-Ramírez MT and Rodríguez-Sánchez IP: The phenotype, psychotype and genotype of bruxism. Biomed Rep 8: 264-268, 2018.
16. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, Bair E, Baraian C, Mack N, Slade GD and Maixner W: Psychological factors associated with development of TMD: The OPPERA prospective cohort study. J Pain 14 (12 Suppl): T75-T90, 2013.
17. Bertoli E, de Leeuw R, Schmidt JE, Okeson JP and Carlson CR: Prevalence and impact of post-traumatic stress disorder symptoms in patients with masticatory muscle or temporomandibular joint pain: Differences and similarities. J Orofac Pain 21: 107-119, 2007.
18. Guidi J, Lucente M, Sonino N and Fava GA: Allostatic load and its impact on health: A systematic review. Psychother Psychosom 90: 11-27, 2021.
19. Tsai CM, Chou SL, Gale EN and McCall WD Jr: Human masticatory muscle activity and jaw position under experimental stress. J Oral Rehabil 29: 44-51, 2002.
20. Manfredini D and Lobbezoo F: Role of psychosocial factors in the etiology of bruxism. J Orofac Pain 23: 153-166, 2009.
21. Herman JP and Mueller NK: Role of the ventral subiculum in stress integration. Behav Brain Res 174: 215-224, 2006.
22. Rosen JB, Fanselow MS, Young SL, Sitcoske M and Maren S: Immediate-early gene expression in the amygdala following footshock stress and contextual fear conditioning. Brain Res 796: 132-142, 1998.
23. Piazza PV and Le Moal M: The role of stress in drug self-administration. Trends Pharmacol Sci 19: 67-74, 1998.
24. Floresco SB, West AR, Ash B, Moore H and Grace AA: Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 6: 968-973, 2003.
25. Lavigne GJ, Kato T, Kolta A and Sessle BJ: Neurobiological mechanisms involved in sleep bruxism. Crit Rev Oral Biol Med 14: 30-46, 2003.
26. Blanchet PJ, Rompré PH, Lavigne GJ and Lamarche C: Oral dyskinesia: A clinical overview. Int J Prosthodont 18: 10-19, 2005.
27. Clark GT and Ram S: Four oral motor disorders: Bruxism, dystonia, dyskinesia and drug-induced dystonic extrapyramidal reactions. Dent Clin North Am 51: 225-243, viii-ix, 2007.
28. Kwak YT, Han IW, Lee PH, Yoon JK and Suk SH: Associated conditions and clinical significance of awake bruxism. Geriatr Gerontol Int 9: 382-390, 2009.
29. Garrett AR and Hawley JS: SSRI-associated bruxism: A systematic review of published case reports. Neurol Clin Pract 8: 135-141, 2018.
30. Okamoto K, Imbe H, Tashiro A, Kimura A, Donishi T, Tamai Y and Senba E: The role of peripheral 5HT2A and 5HT1A receptors on the orofacial formalin test in rats with persistent temporomandibular joint inflammation. Neuroscience 130: 465-474, 2005.
31. Nakanishi O and Ishikawa T: Involvement of peripheral 5-HT2A receptor activation in inflammatory pain. Nihon Rinsho 59: 1675-1680, 2001 (In Japanese).
32. López JF, Vázquez DM, Chalmers DT and Watson SJ: Regulation of 5-HT receptors and the hypothalamic-pituitary-adrenal axis. Implications for the neurobiology of suicide. Ann N Y Acad Sci 836: 106-134, 1997.
33. Yeung LY, Kung HF and Yew DT: Localization of 5-HT1A and 5-HT2A positive cells in the brainstems of control age-matched and Alzheimer individuals. Age (Dordr) 32: 483-495, 2010.
34. İnan R, Şenel GB, Yavlal F, Karadeniz D, Gündüz A and Kiziltan ME: Sleep bruxism is related to decreased inhibitory control of trigeminal motoneurons, but not with reticulobulbar system. Neurol Sci 38: 75-81, 2017.
35. Belujon P and Grace AA: Critical role of the prefrontal cortex in the regulation of hippocampus-accumbens information flow. J Neurosci 28: 9797-9805, 2008.
36. Floresco SB, Blaha CD, Yang CR and Phillips AG: Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: Cellular mechanisms of input selection. J Neurosci 21: 2851-2860, 2001.
37. Valenti O, Gill KM and Grace AA: Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: Response alteration by stress pre-exposure. Eur J Neurosci 35: 1312-1321, 2012.
38. Dunlop BW and Nemeroff CB: The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 64: 327-337, 2007.
39. Ueno Y, Higashiyama M, Haque T, Masuda Y, Katagiri A, Toyoda H, Uzawa N, Yoshida A and Kato T: Motor representation of rhythmic jaw movements in the amygdala of guinea pigs. Arch Oral Biol 135: 105362, 2022.
40. Jie F, Yin G, Yang W, Yang M, Gao S, Lv J and Li B: Stress in regulation of GABA amygdala system and relevance to neuropsychiatric diseases. Front Neurosci 12: 562, 2018.
41. Klausberger T and Somogyi P: Neuronal diversity and temporal dynamics: The unity of hippocampal circuit operations. Science 321: 53-57, 2008.
42. Prager EM, Bergstrom HC, Wynn GH and Braga MF: The basolateral amygdala γ-aminobutyric acidergic system in health and disease. J Neurosci Res 94: 548-567, 2016.
43. Liu ZP, Song C, Wang M, He Y, Xu XB, Pan HQ, Chen WB, Peng WJ and Pan BX: Chronic stress impairs GABAergic control of amygdala through suppressing the tonic GABAA receptor currents. Mol Brain 7: 32, 2014.
44. Quessy F, Bittar T, Blanchette LJ, Lévesque M and Labonté B: Stress-induced alterations of mesocortical and mesolimbic dopaminergic pathways. Sci Rep 11: 11000, 2021.
45. Peña CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, Issler O, Loh YE, Leong T, Kiraly DD, *et al*: Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 356: 1185-1188, 2017.
46. Bagot RC, Cates HM, Purushothaman I, Lorsch ZS, Walker DM, Wang J, Huang X, Schlüter OM, Maze I, Peña CJ, *et al*: Circuit-wide transcriptional profiling reveals brain region-specific gene networks regulating depression susceptibility. Neuron 90: 969-983, 2016.
47. Watanabe M, Narita M, Hamada Y, Yamashita A, Tamura H, Ikegami D, Kondo T, Shinzato T, Shimizu T, Fukuchi Y, *et al*: Activation of ventral tegmental area dopaminergic neurons reverses pathological allodynia resulting from nerve injury or bone cancer. Mol Pain 14: 1744806918756406, 2018.
48. Baliki MN, Geha PY, Fields HL and Apkarian AV: Predicting value of pain and analgesia: Nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 66: 149-160, 2010.
49. Martikainen IK, Nuechterlein EB, Peciña M, Love TM, Cummiford CM, Green CR, Stohler CS and Zubieta JK: Chronic back pain is associated with alterations in dopamine neurotransmission in the ventral striatum. J Neurosci 35: 9957-9965, 2015.
50. Borsook D, Linnman C, Faria V, Strassman AM, Becerra L and Elman I: Reward deficiency and anti-reward in pain chronification. Neurosci Biobehav Rev 68: 282-297, 2016.

51. Ramdani C, Carbonnell L, Vidal F, Béranger C, Dagher A and Hasbroucq T: Dopamine precursors depletion impairs impulse control in healthy volunteers. Psychopharmacology (Berl) 232: 477-487, 2015.
52. Zhao YJ, Liu Y, Wang J, Li Q, Zhang ZM, Tu T, Lei R, Zhang M and Chen YJ: Activation of the mesencephalic trigeminal nucleus contributes to masseter hyperactivity induced by chronic restraint stress. Front Cell Neurosci 16: 841133, 2022.
53. Wall EM and Woolley SC: Acetylcholine in action. Elife 9: e57515, 2020.
54. Miranda-Vilela AL, Akimoto AK, Lordelo GS, Pereira LC, Grisolia CK and Klautau-Guimarães Mde N: Creatine kinase MM TaqI and methylenetetrahydrofolate reductase C677T and A1298C gene polymorphisms influence exercise-induced C-reactive protein levels. Eur J Appl Physiol 112: 183-192, 2012.
55. Boscato N, Exposto F, Nascimento GG, Svensson P and Costa YM: Is bruxism associated with changes in neural pathways? A systematic review and meta-analysis of clinical studies using neurophysiological techniques. Brain Imaging Behav 16: 2268-2280, 2022.
56. Chmieliauskaite M, Stelson EA, Epstein JB, Klasser GD, Farag A, Carey B, Albuquerque R, Mejia L, Ariyawardana A, Nasri-Heir C, *et al*: Consensus agreement to rename burning mouth syndrome and improve international classification of diseases-11 disease criteria: An international Delphi study. Pain 162: 2548-2557, 2021.
57. Jääskeläinen SK: Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol 123: 71-77, 2012.
58. Corsalini M, Di Venere D, Pettini F, Lauritano D and Petruzzi M: Temporomandibular disorders in burning mouth syndrome patients: An observational study. Int J Med Sci 10: 1784-1789, 2013.
59. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A and Sapelli P: Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 115: 332-337, 2005.
60. Forssell H, Jääskeläinen S, Tenovuo O and Hinkka S: Sensory dysfunction in burning mouth syndrome. Pain 99: 41-47, 2002.
61. Kubo KY, Iinuma M and Chen H: Mastication as a Stress-coping behavior. Biomed Res Int 2015: 876409, 2015.
62. Chen H, Iinuma M, Onozuka M and Kubo KY: Chewing maintains hippocampus-dependent cognitive function. Int J Med Sci 12: 502-509, 2015.
63. Mori D, Katayama T, Miyake H, Fujiwara S and Kubo KY: Occlusal disharmony leads to learning deficits associated with decreased cellular proliferation in the hippocampal dentate gyrus of SAMP8 mice. Neurosci Lett 534: 228-232, 2013.
64. Mori D, Miyake H, Mizutani K, Shimpo K, Sonoda S, Yamamoto T, Fujiwara S and Kubo KY: Effects of occlusal disharmony on the hippocampal dentate gyrus in aged senescence-accelerated mouse prone 8 (SAMP8). Arch Oral Biol 65: 95-101, 2016.
65. Azuma K, Ogura M, Kondo H, Suzuki A, Hayashi S, Iinuma M, Onozuka M and Kubo KY: Maternal active mastication during prenatal stress ameliorates prenatal stress-induced lower bone mass in adult mouse offspring. Int J Med Sci 14: 348-355, 2017.
66. Suzuki A, Iinuma M, Hayashi S, Sato Y, Azuma K and Kubo KY: Maternal chewing during prenatal stress ameliorates stress-induced hypomyelination, synaptic alterations, and learning impairment in mouse offspring. Brain Res 1651: 36-43, 2016.
67. Onishi M, Iinuma M, Tamura Y and Kubo KY: Learning deficits and suppression of the cell proliferation in the hippocampal dentate gyrus of offspring are attenuated by maternal chewing during prenatal stress. Neurosci Lett 560: 77-80, 2014.
68. Snyder JS, Soumier A, Brewer M, Pickel J and Cameron HA: Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature 476: 458-461, 2011.
69. Shirasu M, Takahashi T, Yamamoto T, Itoh K, Sato S and Nakamura H: Direct projections from the central amygdaloid nucleus to the mesencephalic trigeminal nucleus in rats. Brain Res 1400: 19-30, 2011.
70. Han W, Tellez LA, Rangel MJ Jr, Motta SC, Zhang X, Perez IO, Canteras NS, Shammah-Lagnado SJ, van den Pol AN and de Araujo IE: Integrated control of predatory hunting by the central nucleus of the amygdala. Cell 168: 311-324.e18, 2017.
71. Kaya B, Geha P, de Araujo I, Cioffi I and Moayedi M: Identification of central amygdala and trigeminal motor nucleus connectivity in humans: An ultra-high field diffusion MRI study. Hum Brain Mapp 44: 1309-1319, 2023.
72. Kolta A, Westberg KG and Lund JP: Identification of brainstem interneurons projecting to the trigeminal motor nucleus and adjacent structures in the rabbit. J Chem Neuroanat 19: 175-195, 2000.
73. Nishigawa K, Bando E and Nakano M: Quantitative study of bite force during sleep associated bruxism. J Oral Rehabil 28: 485-491, 2001.
74. Trulsson M: Sensory-motor function of human periodontal mechanoreceptors. J Oral Rehabil 33: 262-273, 2006.
75. Trulsson M: Force encoding by human periodontal mechanoreceptors during mastication. Arch Oral Biol 52: 357-360, 2007.
76. Trulsson M, Johansson RS and Olsson KA: Directional sensitivity of human periodontal mechanoreceptive afferents to forces applied to the teeth. J Physiol 447: 373-389, 1992.
77. Pang YW, Li JL, Nakamura K, Wu S, Kaneko T and Mizuno N: Expression of vesicular glutamate transporter 1 immunoreactivity in peripheral and central endings of trigeminal mesencephalic nucleus neurons in the rat. J Comp Neurol 498: 129-141, 2006.
78. Ishii T, Suenaga R, Iwata W, Miyata R, Fujikawa R and Muroi Y: Bilateral lesions of the mesencephalic trigeminal sensory nucleus stimulate hippocampal neurogenesis but lead to severe deficits in spatial memory resetting. Brain Res 1342: 74-84, 2010.
79. Yokoyama S, Kinoshita K, Muroi Y and Ishii T: The effects of bilateral lesions of the mesencephalic trigeminal sensory nucleus on nocturnal feeding and related behaviors in mice. Life Sci 93: 681-686, 2013.
80. Andrisani G: Teeth and central nervous system: What happens when you go to sleep. Sleep Med Dis Int J 1: 21-25, 2017.
81. Saper CB, Chou TC and Scammell TE: The sleep switch: Hypothalamic control of sleep and wakefulness. Trends Neurosci 24: 726-731, 2001.
82. Szymusiak R and McGinty D: Hypothalamic regulation of sleep and arousal. Ann N Y Acad Sci 1129: 275-286, 2008.
83. Luppi PH: Neurochemical aspects of sleep regulation with specific focus on slow-wave sleep. World J Biol Psychiatry 11 (Suppl 1): S4-S8, 2010.
84. Zhu J, Li X, Zhu F, Chen L, Zhang C, McGrath C, He F, Xiao Y and Jin L: Multiple tooth loss is associated with vascular cognitive impairment in subjects with acute ischemic stroke. J Periodontal Res 50: 683-688, 2015.
85. Horvath TL, Peyron C, Diano S, Ivanov A, Aston-Jones G, Kilduff TS and van Den Pol AN: Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. J Comp Neurol 415: 145-159, 1999.
86. Okumura T, Takeuchi S, Motomura W, Yamada H, Egashira Si S, Asahi S, Kanatani A, Ihara M and Kohgo Y: Requirement of intact disulfide bonds in orexin-A-induced stimulation of gastric acid secretion that is mediated by OX1 receptor activation. Biochem Biophys Res Commun 280: 976-981, 2001.
87. Satoh Y, Uchida M, Fujita A, Nishio H, Takeuchi T and Hata F: Possible role of orexin A in nonadrenergic, noncholinergic inhibitory response of muscle of the mouse small intestine. Eur J Pharmacol 428: 337-342, 2001.
88. Cruccu G, Frisardi G, Pauletti G, Romaniello A and Manfredi M: Excitability of the central masticatory pathways in patients with painful temporomandibular disorders. Pain 73: 447-454, 1997.
89. Floresco SB: Dopaminergic regulation of limbic-striatal interplay. J Psychiatry Neurosci 32: 400-411, 2007.
90. Belujon P and Grace AA: Regulation of dopamine system responsivity and its adaptive and pathological response to stress. Proc Biol Sci 282: 20142516, 2015.
91. Ono Y, Yamamoto T, Kubo KY and Onozuka M: Occlusion and brain function: Mastication as a prevention of cognitive dysfunction. J Oral Rehabil 37: 624-640, 2010.
92. Hansen PO, Svensson P, Arendt-Nielsen L and Jensen TS: Human masseter inhibitory reflexes evoked by repetitive electrical stimulation. Clin Neurophysiol 113: 236-242, 2002.
93. Onozuka M, Watanabe K, Nagasaki S, Jiang Y, Ozono S, Nishiyama K, Kawase T, Karasawa N and Nagatsu I: Impairment of spatial memory and changes in astroglial responsiveness following loss of molar teeth in aged SAMP8 mice. Behav Brain Res 108: 145-155, 2000.
94. Kubo KY, Yamada Y, Iinuma M, Iwaku F, Tamura Y, Watanabe K, Nakamura H and Onozuka M: Occlusal disharmony induces spatial memory impairment and hippocampal neuron degeneration via stress in SAMP8 mice. Neurosci Lett 414: 188-191, 2007.
95. Proietti R, Mapelli D, Volpe B, Bartoletti S, Sagone A, Dal Bianco L and Daliento L: Mental stress and ischemic heart disease: evolving awareness of a complex association. Future Cardiol 7: 425-437, 2011.

96. Reber SO: Stress and animal models of inflammatory bowel disease-an update on the role of the hypothalamo-pituitary-adrenal axis. Psychoneuroendocrinology 37: 1-19, 2012.
97. Furuzawa M, Chen H, Fujiwara S, Yamada K and Kubo KY: Chewing ameliorates chronic mild stress-induced bone loss in senescence-accelerated mouse (SAMP8), a murine model of senile osteoporosis. Exp Gerontol 55: 12-18, 2014.
98. van Selms MK, Lobbezoo F, Visscher CM and Naeije M: Myofascial temporomandibular disorder pain, parafunctions and psychological stress. J Oral Rehabil 35: 45-52, 2008.
99. Di Paolo C, Costanzo GD, Panti F, Rampello A, Falisi G, Pilloni A, Cascone P and Iannetti G: Epidemiological analysis on 2375 patients with TMJ disorders: Basic statistical aspects. Ann Stomatol (Roma) 4: 161-169, 2013.
100. Safari A, Jowkar Z and Farzin M: Evaluation of the relationship between bruxism and premature occlusal contacts. J Contemp Dent Pract 14: 616-621, 2013.
101. Fritzen VM, Colonetti T, Cruz MVB, Ferraz SD, Ceretta L, Tuon L, DA Rosa MI and Ceretta RA: Levels of salivary cortisol in adults and children with bruxism diagnosis: A systematic review and meta-analysis. J Evid Based Dent Pract 22: 101634, 2022.
102. Chung S, Son GH and Kim K: Circadian rhythm of adrenal glucocorticoid: Its regulation and clinical implications. Biochim Biophys Acta 1812: 581-591, 2011.
103. Glaros AG, Williams K and Lausten L: The role of parafunctions, emotions and stress in predicting facial pain. J Am Dent Assoc 136: 451-458, 2005.
104. Leistad RB, Sand T, Westgaard RH, Nilsen KB and Stovner LJ: Stress-induced pain and muscle activity in patients with migraine and tension-type headache. Cephalalgia 26: 64-73, 2006.
105. de Leeuw R, Schmidt JE and Carlson CR: Traumatic stressors and post-traumatic stress disorder symptoms in headache patients. Headache 45: 1365-1374, 2005.
106. Rompré PH, Daigle-Landry D, Guitard F, Montplaisir JY and Lavigne GJ: Identification of a sleep bruxism subgroup with a higher risk of pain. J Dent Res 86: 837-842, 2007.
107. Camparis CM, Formigoni G, Teixeira MJ, Bittencourt LR, Tufik S and de Siqueira JT: Sleep bruxism and temporomandibular disorder: Clinical and polysomnographic evaluation. Arch Oral Biol 51: 721-728, 2006.
108. Rossetti LM, Pereira de Araujo Cdos R, Rossetti PH and Conti PC: Association between rhythmic masticatory muscle activity during sleep and masticatory myofascial pain: A polysomnographic study. J Orofac Pain 22: 190-200, 2008.
109. Lavigne GJ, Rompré PH, Poirier G, Huard H, Kato T and Montplaisir JY: Rhythmic masticatory muscle activity during sleep in humans. J Dent Res 80: 443-448, 2001.
110. Miyake H, Mori D, Katayama T, Fujiwara S, Sato Y, Azuma K and Kubo KY: Novel stress increases hypothalamic-pituitary-adrenal activity in mice with a raised bite. Arch Oral Biol 68: 55-60, 2016.
111. Aizawa H, Cui W, Tanaka K and Okamoto H: Hyperactivation of the habenula as a link between depression and sleep disturbance. Front Hum Neurosci 7: 826, 2013.
112. Gameiro GH, da Silva Andrade A, Nouer DF and Ferraz de Arruda Veiga MC: How may stressful experiences contribute to the development of temporomandibular disorders? Clin Oral Investig 10: 261-268, 2006.
113. Liu X, Zhou KX, Yin NN, Zhang CK, Shi MH, Zhang HY, Wang DM, Xu ZJ, Zhang JD, Li JL and Wang MQ: Malocclusion generates anxiety-like behavior through a putative lateral habenula-mesencephalic trigeminal nucleus pathway. Front Mol Neurosci 12: 174, 2019.
114. Kubo KY, Huayue C and Onozuk M: The relationship between mastication and cognition. Senescence and Senescence-Related Disorders, 2013.
115. Onozuka M, Hirano Y, Tachibana A, Kim W, Ono Y, Sasaguri K, Kubo K, Niwa M, Kanematsu K and Watanabe K: Interactions between chewing and brain activity in humans. In: Novel Trends in Brain Science: Brain Imaging, Learning and Memory, Stress and Fear, and Pain. Onozuka M and Yen CT (eds). Springer Japan, Tokyo, pp99-113, 2008.
116. Ichihashi Y, Arakawa Y, Iinuma M, Tamura Y, Kubo KY, Iwaku F, Sato Y and Onozuka M: Occlusal disharmony attenuates glucocorticoid negative feedback in aged SAMP8 mice. Neurosci Lett 427: 71-76, 2007.
117. Miura H, Kariyasu M, Yamasaki K, Arai Y and Sumi Y: Relationship between general health status and the change in chewing ability: A longitudinal study of the frail elderly in Japan over a 3-year period. Gerodontology 22: 200-205, 2005.
118. Watanabe K, Ozono S, Nishiyama K, Saito S, Tonosaki K, Fujita M and Onozuka M: The molarless condition in aged SAMP8 mice attenuates hippocampal Fos induction linked to water maze performance. Behav Brain Res 128: 19-25, 2002.
119. Onozuka M, Watanabe K, Fujita M, Tonosaki K and Saito S: Evidence for involvement of glucocorticoid response in the hippocampal changes in aged molarless SAMP8 mice. Behav Brain Res 131: 125-129, 2002.
120. Kubo KY, Iwaku F, Watanabe K, Fujita M and Onozuka M: Molarless-induced changes of spines in hippocampal region of SAMP8 mice. Brain Res 1057: 191-195, 2005.
121. Aoki H, Kimoto K, Hori N, Hoshi N, Yamamoto T and Onozuka M: Molarless condition suppresses proliferation but not differentiation rates into neurons in the rat dentate gyrus. Neurosci Lett 469: 44-48, 2010.
122. Iinuma M, Kondo H, Kurahashi M, Ohnishi M, Tamura Y, Caen H and Kubo KY: Relationship between the early toothless condition and hippocampal functional morphology. Anat Physiol 4: 1000149, 2014.
123. Onozuka M, Watanabe K, Mirbod SM, Ozono S, Nishiyama K, Karasawa N and Nagatsu I: Reduced mastication stimulates impairment of spatial memory and degeneration of hippocampal neurons in aged SAMP8 mice. Brain Res 826: 148-153, 1999.
124. Kubo KY, Kojo A, Yamamoto T and Onozuka M: The bite-raised condition in aged SAMP8 mice induces dendritic spine changes in the hippocampal region. Neurosci Lett 441: 141-144, 2008.
125. Katayama T, Mori D, Miyake H, Fujiwara S, Ono Y, Takahashi T, Onozuka M and Kubo KY: Effect of bite-raised condition on the hippocampal cholinergic system of aged SAMP8 mice. Neurosci Lett 520: 77-81, 2012.
126. Chaouloff F: Regulation of 5-HT receptors by corticosteroids: Where do we stand? Fundam Clin Pharmacol 9: 219-233, 1995.
127. Hikosaka O: The habenula: From stress evasion to value-based decision-making. Nat Rev Neurosci 11: 503-513, 2010.
128. Shelton L, Becerra L and Borsook D: Unmasking the mysteries of the habenula in pain and analgesia. Prog Neurobiol 96: 208-219, 2012.
129. Boulos LJ, Darcq E and Kieffer BL: Translating the habenula-from rodents to humans. Biol Psychiatry 81: 296-305, 2017.
130. Ohara H, Tachibana Y, Fujio T, Takeda-Ikeda R, Sato F, Oka A, Kato T, Ikenoue E, Yamashiro T and Yoshida A: Direct projection from the lateral habenula to the trigeminal mesencephalic nucleus in rats. Brain Res 1630: 183-197, 2016.
131. Li K, Zhou T, Liao L, Yang Z, Wong C, Henn F, Malinow R and Yates JR III, Hu H: βCaMKII in lateral habenula mediates core symptoms of depression. Science 341: 1016-1020, 2013.
132. Jacinto LR, Mata R, Novais A, Marques F and Sousa N: The habenula as a critical node in chronic stress-related anxiety. Exp Neurol 289: 46-54, 2017.
133. Luco K: The relationship of the trigemino-cardiac reflex to sleep bruxism. Lupine Publishers LLC, Online Journal of Neurobiology and Brain Disorders, 2018.
134. Keskinruzgar A DDS, Kalenderoglu A MD, Yapici Yavuz G DDS, Koparal M DDS, Simsek A MD, Karadag AS MD and Utkun M DDS: Investigation of neurodegenerative and inflammatory processes in sleep bruxism. Cranio 38: 358-364, 2020.
135. Kalenderoglu A, Sevgi-Karadag A, Celik M, Egilmez OB, Han-Almis B and Ozen ME: Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? Compr Psychiatry 67: 66-72, 2016.
136. Kalenderoglu A, Çelik M, Sevgi-Karadag A and Egilmez OB: Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. J Affect Disord 204: 159-165, 2016.
137. Minakuchi H, Fujisawa M, Abe Y, Iida T, Oki K, Okura K, Tanabe N and Nishiyama A: Managements of sleep bruxism in adult: A systematic review. Jpn Dent Sci Rev 58: 124-136, 2022.
138. Bhattacharjee B, Saneja R, Bhatnagar A and Gupta P: Effect of dopaminergic agonist group of drugs in treatment of sleep bruxism: A systematic review. J Prosthet Dent 127: 709-715, 2022.