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Review

Adverse effects of the bite-raised condition in animal studies: A systematic review

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ABSTRACT

Objective: To provide a systematic review of the effects of the bite-raised condition in animal models, a widespread technique in modern orthodontics.
Design: A systematic review of the literature was conducted. Original articles were searched through Pubmed, Cochrane Central database and Embase until December 2018.
Results: 242 articles were identified through database searching. After removing the duplicates, 198 articles were screened by reviewing the abstracts. 27 full text articles were assessed for eligibility and, after 7 exclusions, 20 articles were included in the review process. Studies selected by the review process concerned animal models. Histological, molecular, biochemical and electromyographical studies were evaluated. The results, with a high level of agreement in different animals, showed that the bite-raised condition is a source of stress, inducing increased plasma corticosterone, urinary cortisol and HPA axis alterations; it predisposes the organism to react to subsequent stressful stimulation with a significantly greater incretion of glucocorticoids, thus inducing hypersensitivity to novel forms of stress; it affects the structure of the hippocampus, reducing the number of neurons, increasing the number of glial cells and worsening memory and spatial orientation; it alters the electromyographical activity of masticatory muscles.
Conclusions: The results of research conducted on animal models do not necessarily apply directly to human beings. More clinical research, with special attention to adolescent patients, is necessary to clarify whether, in humans, the bite-raised condition is accompanied by adverse effects comparable to those observed in animals.

1. Introduction

The relationships between the central nervous system (CNS) and the masticatory function has been investigated in the recent past and is of interest in the neurological and dental fields. The relationship between chewing and the central nervous system is of considerable importance, during both growing and ageing. While it is well known that the motor control of the masticatory function involves the majority of the structures of the central nervous system including brainstem, basal nuclei, midbrain, cerebellum and cortex, its influence on the hippocampus, memory and cognitive activity has only recently emerged (Piancino & Kyrkanides, 2016). The disruption of the masticatory function has effects in subjects of all ages and appears to affect mainly the hippocampus: young, middle-aged and senile mice subjected to masticatory imbalances show a reduced number of neurons in CA1 and CA3 and an increased number of hypertrophic astrocytes in CA1 (Fukushima-Nakayama et al., 2017). All these changes seem to be aggravated by aging and after tooth loss, suggesting additive effects. In order to alter the masticatory function, different animal models have been exposed to different experimental conditions: modified diet, removal of molar teeth (Kubo et al., 2017) or occlusal disharmony obtained by means of a bite-raising procedure. These approaches revealed that masticatory dysfunction, in addition to the already cited effects on the number of neurons, impairs spatial learning and memory in water maze tests in rats and mice, and that these deficits seem to worsen with aging (Tada & Miura, 2017).

Unfortunately, raising the bite is a trick widely used in orthodontics, in both developing and ageing patients. Its popularity is a consequence of a technical issue, that is to avoid contacts between the upper and lower teeth. For this reason, it is used in association with fixed

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appliances to prevent the detachment of the lower brackets. In order to raise the bite, lumps of hard resin are usually positioned on the lower and/or upper first molars, the most important masticatory teeth, suddenly preventing the occlusal contacts that are usually present between the upper and lower arches. The need for such a review stems from the increasing popularity of various forms of bite-raising and their application in both young and adult patients.

The interest of the bite-raised condition's consequences on the central nervous system is to avoid neural side effects during orthodontic therapy. The aim of this systematic review is to evaluate its morphological effects, especially in the region of the hippocampus, hormonal changes on the hypothalamic-pituitary-adrenal axis, and behavioral outcomes as have emerged in studies in animals. To complete the picture, the electromyographical effects on the masticatory muscles in bite-raised condition have been included as well.

2. Materials & methods

Search strategy

A systematic review of the literature was conducted. Original articles were searched through Pubmed, Cochrane central database and Embase until December 2018.

The research has been done with the following free words: occlusal disharmony, bite-rais*; bite-rais* AND EMG; with the following MESH Terms: ((("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ("Mice"[Mesh] OR mice)) AND ("Hippocampus"[Mesh] OR hippocampus), ((("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ("Mice"[Mesh] OR mice)) AND ((("Hippocampus"[Mesh] OR hippocampus)) OR ((("Maze Learning"[Mesh] OR maze learning*)) OR ("Spatial Learning"[Mesh] OR spatial learning*))), (("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ("Hippocampus"[Mesh] OR hippocampus) ((("Rats"[Mesh] OR rat OR rats)) AND ("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ("Hippocampus"[Mesh] OR hippocampus), ((("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ((("Maze Learning"[Mesh] OR maze learning*)) OR ("Spatial Learning"[Mesh] OR spatial learning*))) AND ((("Rats"[Mesh] OR rat OR rats))); with the following clinical query: (Medical Genetics[filter]) AND ((("Bite Force"[Mesh] OR bite force* OR occlusal force* OR malocclusion* OR masticatory force* OR masticat* OR resin bite*)) AND ("Hippocampus"[Mesh] OR hippocampus)).

Additional studies were taken from reference lists of previous review articles and citations of relevant original articles were screened. The "related articles" tool was used to improve the PubMed searches, and references of included studies was checked by a research librarian. Unpublished studies, grey literature or studies not published in English were excluded.

3. Results

Search results

242 articles were identified through database searching. After removing the duplicates, 198 articles were screened by reviewing the abstracts. 27 full text articles were assessed for eligibility and, after 7 exclusions, 20 articles were included in the review process as reported in Fig. 1. A few articles were excluded because they investigated forms of occlusal instability other than raising the bite (e.g. molarless mice, selective abrasion of crowns); others were excluded because, even though they concerned bite-raised animals, other variables than masticatory muscles electromyography were considered. One, though pertinent to the topic in question, was excluded on the basis of being a clinical study in humans.

Type of selected studies

Studies selected by the review process may be divided in molecular studies (Budtz-Jørgensen, 1981); (Kubo et al., 2007), (Kubo, Kojo, Yamamoto, & Onozuka, 2008); (Iinuma et al., 2008); (Arakawa et al., 2007); (Ichihashi et al., 2007), (Ichihashi et al., 2008); (Kubo, Saitoh et al., 2008); (Iinuma et al., 2008); (Kojo, Yamada, Kubo, Yamashita, & Yamamoto, 2010); (Miyake et al., 2011), (Miyake et al., 2016); (Katayama et al., 2012); (Mori, Katayama, Miyake, Fujiwara, & Kubo, 2013), (Mori et al., 2016); (Yamada, Ono, Kubo, Yamamoto, & Onozuka, 2013); (Tang, Li, Jiang, Han, & Yao, 2017); and electromyographical studies (Yaffe, Tal, & Ehrlich, 1991); (Matsuka, Kitada, Mitoh, Adachi, & Yamashita, 1998); (Kanayama et al., 2011).

4. Discussion

In this review of the literature, we evaluated the known effects of the bite-raised condition when it is experimentally implemented in a variety of animal models. This condition abruptly alters the customary occlusion, suddenly eliminating all dental contact points except for two or three (if a tripod configuration is used), that turn out in tooth overloading. The proprioceptive information originating from most of the periodontal mechanoreceptors is therefore lost, except those associated with the teeth involved in the bite-raising procedure, which are subjected to much greater strain than usual. The strength developed by the masticatory muscles, as a result of the presence of the bite-raising appliance, is concentrated in a very narrow area, instead of being evenly distributed on the occlusal surfaces. (Table 1)

To our knowledge, the wide-ranging effects of the bite-raised condition have never been systematically reviewed in the past. Over the following discussion, we shall describe and evaluate the literature reviewed in four sections, pertaining respectively (a) the connection between the bite-raised condition and stress, (b) its effect on the trophism of the hippocampus, (c) alteration in the electromyographical activity of masticatory muscles and (d) a comment of the salient clinical issues potentially correlated with this technique.

4.1. The bite-raised condition and stress

4.1.1. Hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA) axis responds to a variety of stressful stimuli by increasing the plasma concentration of glucocorticoids (Azuma, Zhou, Niwa, & Kubo, 2017). The main glucocorticoids released in response to stress are corticosterone in rodents and cortisol in primates (Iinuma et al., 2008). The HPA axis is negatively regulated by glucocorticoids (GCs) at different levels, including the anterior pituitary gland, hypothalamus, hippocampus and amygdale (Ichihashi et al., 2007); the hypothalamic paraventricular nucleus receives afferent inputs from these regions, among others, and, in response, releases corticotropin-releasing hormone (CRH) and arginine vasopressine (AVP) in the hypothalamic median eminence, where they enter the pituitary portal system and stimulate the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. Circulating ACTH in turn stimulates the synthesis and release of GCs from the adrenal cortex (Azuma et al., 2017).

In this review of the literature, all the Authors agree that the bite-raised condition, in animal models with different characteristics and ages, acts as a stressful stimulus and activates the HPA axis. In primates, raising the bite determined both an increase of urinary cortisol and a reduction in body weight (Budtz-Jørgensen, 1981). In Wistar rats, the positioning of acrylic caps on the lower incisors induced an increase in the concentration of extracellular noradrenaline in the hypothalamic paraventricular nucleus, which stimulates the HPA axis, and plasma corticosterone (Yoshihara, Matsumoto, & Ogura, 2001). In the same animal model, a metal crown placed on the right maxillary molar determined an increase of plasma corticosterone, among other alterations (Tang et al., 2017). In the aged senescence-accelerated prone mice

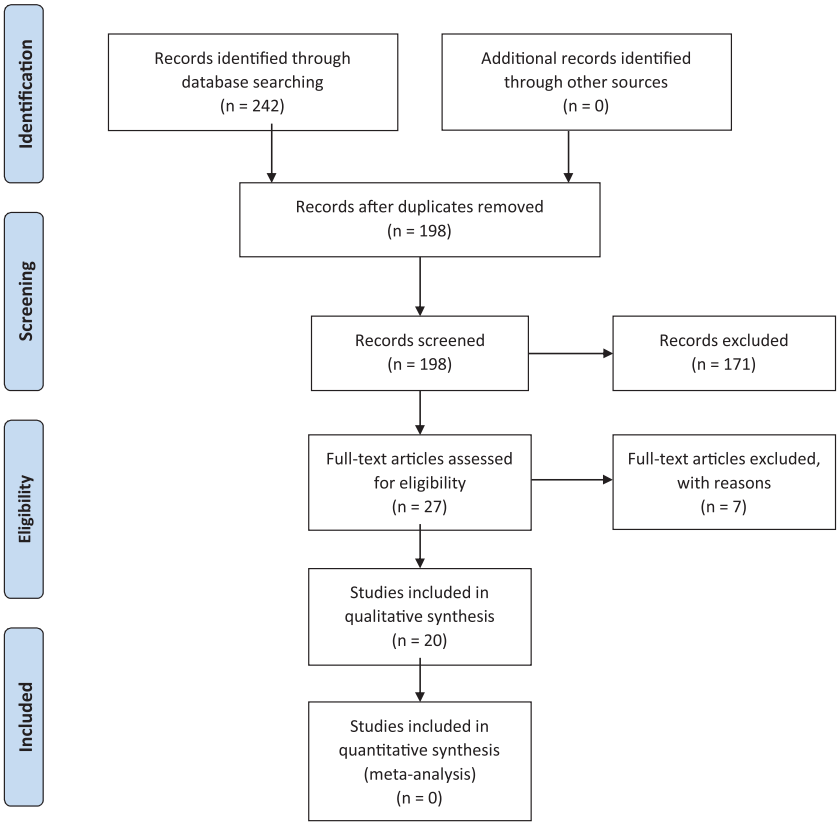

Fig. 1. Flow-chart according to PRISMA statements.

(SAMP8), the bite-raising procedure was shown to increase plasma corticosterone level and to reduce the expression of glucocorticoid receptor and its mRNA in the hippocampus (Ichihashi et al., 2007); (Iinuma et al., 2008). In a different research conducted on the same animal, the bite-raised condition was accompanied by a rapid increase in the expression of CRH mRNA and a slower increase in the expression of AVP mRNA in the parvocellular hypothalamic PVN (Miyake et al., 2016).

4.1.2. Behavioural tests

In addition to the effects of the bite-raised condition on the hypothalamus-pituitary-adrenal axis, regarding which there is agreement among the Authors, several studies evaluated its impact on behaviour. In this review of the literature, three behavioural tests used on mice and rats were found: the Morris water maze (Kubo et al., 2007), (Kubo, Kojo et al., 2008); (Ichihashi et al., 2007); (Iinuma et al., 2008); (Mori et al., 2013); (Yamada et al., 2013), the open field test and the elevated plus maze test (Tang et al., 2017).

The Morris water maze test is a sensitive behavioural assay for brain abnormalities, especially for the hippocampus, and has long been regarded as a hippocampal dependent task based on studies of special impairment after selective lesioning of the hippocampus (Yamada et al., 2013); it is commonly used to examine spatial cognitive ability related to hippocampal function (Iinuma et al., 2008).

The test is carried out by means of a circular stainless steel tank, 90 cm in diameter and 30 cm deep, filled with water at 28 °C to a height of 22 or 23 cm; the water is covered with floating polystyrene foam granules (approximately 2 mm in diameter) and a platform is submerged 1 cm under the surface of the water at a constant location near the centre of one of the four quadrants of the pool. The mice are in turn placed gently in the water from one of four points around the perimeter of the tank and given 4 trials a day for 7 consecutive days (a total of 28 trials), with the sequence of starting positions randomly changed every day. Swim paths, distances and latencies to reach the platform are monitored by a video camera linked to a computer. The mice initially swim randomly about, until, by chance, they encounter the platform. With training, the mice learn the platform's position, according to its relation to the visual clues present around it in the room where the experiment takes place. Consequently, the time required to reach the platform decreases gradually.

The results of the test are dependent on both the age of the bite-raised mice and the duration of the bite-raised condition. The latency is increased in a significant way, i.e., the mouse requires more time to find the platform, only in the 9-month-old bite-raised mice when compared to controls. As spatial cognitive ability decreases with age, these findings indicate that this age-related impairment is further enhanced by the bite-raised condition (Iinuma et al., 2008). It is interesting to observe that the latency to reach the platform in the 9-month-old bite-raised mice becomes greater the longer the bite-raised condition lasts, with a significant difference between 8 and 22 days after the bite-raising operation (Arakawa et al., 2007).

The results of the Morris water maze test demonstrate that in aged SAMP8 mice the bite-raised condition induces behavioural deficits, which are dependent upon its duration.

The open field test and the elevated plus maze test were used to assess locomotor and exploratory activities as well as motivation and anxiety behaviour in a novel environment in rats (Tang et al., 2017). In this experiment, the bite-raised condition was studied in the context of exposure to psychological stress induced by an experimental apparatus. Psychological stress had a greater impact on test scores compared to other experimental variables; among the groups not exposed to psychological stress, the rats with the raised bite achieved lower scores than the control group. The difference tended to worsen with time, i.e. at day 35 after the bite-raising procedure.

Table 1
Characteristics of included studies on the bite-raised condition.

References	Type of study	Animal model	Bite-raising device	Marker analyzed	Type of structures analyzed	Type of analysis	Results
Molecular studies							
(Budtz-Jørgensen, E., 1981)	Molecular	Macaca irus monkeys	Gold occlusal cap splints on molar and premolar teeth, bilaterally	Urinary cortisol; urinary volume; body weight	Hypothalamus-pituitary-adrenal axis	Competitive protein-binding analysis	Urinary cortisol excretion rates were significantly elevated throughout the experimental period; they declined to basal values when the splints were removed.
(Yoshihara et al., 2001)	Molecular	Rats (Wistar)	Acrilic caps on both lower incisors	Plasma corticosterone; Extracellular noradrenaline	Plasma; Hypothalamus	Microdialysis (quantitative)	Significant increase in both plasma corticosterone and PV noradrenaline.
(Kubo et al., 2007)	Molecular, histological and behavioural	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Plasma corticosterone; hippocampal pyramidal neurons	Hippocampal CA3 region	Plasma corticosterone (biochemical); Nissl staining (histological); Morris water maze (behavioural)	An age-related deficit was induced in spatial learning, with a concomitant decrease in the number of hippocampal pyramidal cells.
(Arakawa et al., 2007)	Histological and behavioural	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Hippocampal CA3 cells	Hippocampal CA3 region	Number of hippocampal neurons (quantitative); Morris water maze (behavioural)	The number of hippocampal neurons decreased after the procedure and continued to decrease with time; both the behavioural and the morphologic changes were dependent on the duration of the bite-raised condition.
(Ichihashi et al., 2007)	Molecular and behavioural	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Glucocorticoid receptor	Hippocampal CA1, CA3 and DG regions	In situ hybridisation (molecular); immunohistochemistry; Morris water maze (behavioural)	Reduction of hippocampal GR and GRmRNA expression, leading to HPA axis impairment
(Ichihashi et al., 2008)	Molecular	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Glucocorticoid receptor	Hippocampal dentate gyrus, dorsal and ventral CA1 regions	Immunohistochemical	Reduced expression of GRs in both the dorsal and ventral regions of the hippocampus, impairment of the HPA axis and cognitive function.
(Iinuma et al., 2008)	Molecular, histological and behavioural	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Plasma corticosterone, Fos protein, hippocampal neuron number, GC and GCmRNA	Hippocampal CA1, CA3 and DG regions	Plasma corticosterone (biochemical); Nissl staining (histological); Morris water maze (behavioural); Fos protein induction (molecular); GR and GRmRNA (immunohistochemical and molecular); metirapone (GCs synthesis inhibitor).	Increased blood GC concentration; downregulation of GRmRNA and GR; reduced number of neurons in CA3; decreased number of Fos-positive cells in CA1.
(Kubo, Saitoh et al., 2008)	Molecular and histological	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Hippocampal neurons; GFAP-immunoreactive cells (Glial Fibrillary Acidic Protein)	Hippocampal dentate gyrus, CA1 and CA3 regions	Number of hippocampal neurons in the stratum pyramidalis (quantitative)	Reduced number of hippocampal neurons and increased expression of GFAP-immunoreactive astrocytes.
(Kubo, Kojo et al., 2008)	Histological	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Dendritic spines	Hippocampal CA1 region	Number of spines/50 μm (Golgi-Cox staining); Morris water maze (behavioural)	Reduced learning ability and lower number of CA1-pyramidal cell dendritic spines.
(Kojo et al., 2010)	Molecular	Mice (ddY)	0,1 mm UV-polymerisation resin on maxillary molars	Iba-1 (Ionized calcium-binding adaptor molecule 1, a marker for microglia)	Hippocampal CA1 and DG regions	Immunohistochemical	3 days after the procedure, the areas occupied by microglia in the hippocampal CA1 region increased, but not in the DG.
(Miyake et al., 2011)	Molecular	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Fos protein	Hypothalamic PVN	Immunohistochemistry	Increased number of Fos-positive cells in the PVN 90 minutes after the procedure; the expression of Fos in the PVN adapts relatively quickly to the bite-raised condition.
(Katayama et al., 2012)	Molecular	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Ach and ChAT-positive cholinergic cells	Septohippocampal cholinergic system	Microdialysis (quantitative) and immunohistochemistry	Decreased acetylcholine release in the hyppocampus and reduced number of choline acetyltransferase-immunopositive neurons in the medial septal nucleus.

(*continued on next page*)

Table 1 (*continued*)

References	Type of study	Animal model	Bite-raising device	Marker analyzed	Type of structures analyzed	Type of analysis	Results
(Mori et al., 2013)	Molecular and behavioural	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	BrdU-labeled cells	Hippocampal dentate gyrus (DG)	Morris water maze (behavioural); immunohistochemistry	Cell proliferation in the DG abruptly decreased immediately after raising the procedure; increased gradually within 2 weeks, but did not reach control levels; learning-induced cell proliferation was impaired.
(Yamada et al., 2013)	Molecular and behavioural	Mice (ddY)	0,1 mm UV-polymerisation resin on maxillary molars	Dynorphin A	Hippocampus and amygdala	Immunohistochemistry; immunosorbent assay (ELISA); Morris water maze	Occlusal disharmony caused stress resulting in a transient increase of dynorphin A levels at least in the amygdala, that transiently impaired learning and memory.
(Miyake et al., 2016)	Molecular	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars; restraint stress	CRH and AVP mRNAs	Hypothalamic PVN	In situ hybridisation	Rapid CRH mRNA response and a slower AVP mRNA response in the hypothalamic parvocellular PVN; exposure to a novel stress further reinforced the CRH stress response.
(Mori et al., 2016)	Molecular	Mice (SAMP8)	0,1 mm UV-polymerisation resin on maxillary molars	Newborn cell proliferation, survival, differentiation and apoptosis; BDNF (brain-derived neurotrophic factor)	Hippocampal dentate gyrus	Molecular and immunohistochemical	Decreased neurogenesis, increased apoptosis in the DG and decreased hippocampal BDNF expression.
(Tang et al., 2017)	Molecular and behavioural	Rats (Sprague-Dawley)	Nickel-chromium crown on the right maxillary molar	Serum corticosterone; 5-HT and 5-HT2AR	Prefrontal cortex; hipocampal CA1 and DG regions	Serum corticosterone (biochemical); 5-HT and 5-HT2AR (immunohistochemistry); Open-field test and elevated plus maze test (behavioural)	Occlusal disharmony may be a promoting factor for anxiety through both peripheral and central pathways via the HPA axis and the 5-HT system.
EMG studies							
(Yaffe et al., 1991)	Electromyographical and histological	Male Sabra rats	1-1.5 mm dental composite built up on upper molars, bilaterally	EMG; hystochemical profile of masseterine muscle fibres; morphometry of neuromuscular junctions;	Deep masseter muscle	Electromyographical; histochemical; histological	Initially transient changes; after 7 days of the bite-raised condition, all animals exhibited a decreased EMG activity.
(Matsuka et al., 1998)	Electromyographical	Domestic male rabbits	0,5 mm metal bite-raising splints on the upper molar teeth on both sides of the jaw.	Integral electromyographical activity (microVs); masticatory cycle duration (ms)	Masseter and digastric muscles	Electromyographical	The activity of the masseter muscles was significantly reduced, while the activity of the digastric muscles showed significant increase.
(Kanayama et al., 2011)	Electromyographical	Guinea pigs	Resin bite-raising appliance on lower incisors, increasing inter-molar space by 3 mm	Integral electromyographical activity (microVs); burst duration (ms); total cycle length	Masseter and digastric muscles	Electromyographical	Increased activity of both the masseter and the digastric muscles; the removal of the appliance was not shown to allow these muscles to return to normal conditions.

4.1.3. A stressor and a risk factor for hypersensitivity to novel forms of stress

Raising the bite is a stressful condition and its impact may be measured by the concentration of serum corticosterone, the main glucocorticoid hormone released in rats and mice. It is interesting to compare the effect of the occlusal disharmony induced by raising the bite to those mediated by other conditions, such as psychological stress or the stress of undergoing the surgical procedures (anesthesia, manipulation of the oral cavity etc.) necessary to position a device to raise the bite (as in control groups). Tang and colleagues, studying the serum corticosterone concentration of seven groups of rats, found that, although psychological stress had a greater effect, rats in the bite-raised condition had significantly higher corticosterone levels than controls.

These results indicate that the bite-raised condition acts as a stressor independently of the procedures necessary to put it in place, which, in turn, act as stressful stimuli. They also suggest that the bite-raised condition acts synergistically with psychological stress to determine an even greater activation of the HPA axis (Tang et al., 2017).

To investigate the effect of a novel stressful situation on subjects already in a proven condition of stress, Miyake and colleagues conducted an experiment on 8-month-old, bite-raised SAMP8 mice. The bite-raised condition was shown to activate the HPA axis by means of a rapid CRH (corticotropin-releasing hormone) and a slower AVP (arginine vasopressin) release in the PVN (hypothalamic paraventricular nucleus), suggesting that this form of occlusal disharmony acts as a chronic source of stress for the organism. While CRH expression rapidly increased after the bite-raising procedure, but quickly returned to control levels, the raise in AVP was much slower and this hormone's levels remained elevated longer. Moreover, if, after 14 days of the bite-raised condition, when the CRH concentration had returned to the level of controls and thus the acute stress phase had ended, the bite-raised mice were subjected to a novel form of stress (being placed in a plastic tube without the possibility of lateral movement and under a bright light), the levels of CRH increased to significantly higher levels than controls (Miyake et al., 2016).

The bite-raised condition is, therefore, both a cause of acute and chronic stress and, more importantly, reduces the ability of the organism to face new stressful events. In conclusion, the bite-raised condition is likely to act not only as a risk factor for hypersensitivity to novel forms of stress, but to increase the vulnerability to stressful conditions.

4.2. The bite-raised condition and neural alterations

4.2.1. Loss of neurons and glial activation

In mammals, including humans, new cells are continuously generated in the subgranular layer of the hippocampal dentate gyrus and forebrain subventricular zone. It is established that chronic stress disrupts the generation, survival and differentiation of new-born cells; the increase in glucocorticoid levels, also an effect of exposure to chronic stress, leads to apoptosis (Mori et al., 2016). In the aged SAMP8 mice, the bite-raised condition leads to a reduction of cell proliferation, differentiation and survival, as well as increased apoptosis, glial cell proliferation and a reduction in the expression of brain-derived neurotrophic factor (Arakawa et al., 2007); (Iinuma et al., 2008); (Kubo et al., 2007), (Kubo, Saitoh et al., 2008); (Kojo et al., 2010); (Mori et al., 2013), (Mori et al., 2016).

The number of hippocampal pyramidal cells, assessed by means of Nissl staining, is significantly decreased in the CA3 and DG regions (Kubo et al., 2007), (Kubo, Saitoh et al., 2008). The reduction is dependent on the duration of the bite-raised condition (Arakawa et al., 2007). While a reduction in the number of hippocampal pyramidal cells is a physiological event that accompanies the ageing process, the stress of the bite-raised condition appears to enhance the loss of neurons and to lead to the impairment of spatial memory (Iinuma et al., 2008).

In the subgranular layer of the dentate gyrus, at the border between the granule cell layer and the hilus, the bite-raised condition leads to a reduction of cell proliferation and survival of newborn cells, as well as a significant increase in apoptosis (likely due either to a rapid but short-lasting upregulation of turnover in the entire subgranular zone or to compensatory cell death that counteracts new cell birth).

In the central nervous system, brain-derived neurotrophic factor (BDNF) affects all levels of cell generation, proliferation, survival and differentiation; its expression is highest in the hippocampus. BDNF is essential for neuronal survival and, specifically, for the neuronal population that is continuously regenerated in the brain. Both acute and chronic stress decrease hippocampal BDNF expression. In the bite-raised mouse, BDNF hippocampal expression is significantly reduced and this could account for the impaired cell proliferation, survival and differentiation described in the hippocampus of these animals (Mori et al., 2016).

Microglial cells are the professional phagocytes of the brain and help orchestrate the immunological response by interacting with infiltrating immune cells. During embryogenesis, they originate from a pool of primitive macrophages from the yolk sack; while circulating monocytes do enter the CNS in the course of pathological conditions, recent evidence indicates that the intrinsic pool of microglia replaces the microglia population if depleted. Microglial cells are involved in essentially all brain disease, ranging from neurodegenerative disorders such as Alzheimer's disease, traumatic brain injury such as spinal cord lesions, and psychiatric diseases such as schizophrenia (Wolf, Boddeke, & Kettenmann, 2016). Microglial cells undergo morphological changes when they become activated in a variety of pathological conditions; it is likely that microglial cells respond, directly or indirectly, to elevated levels of serum corticosterone, as in conditions of chronic stress. An increased microglial activity was reported in the cornu ammonis 1 (CA1) region of bite-raised ddY mice but not in the dentate gyrus (DG), probably because of the different characteristics of this latter hippocampal region, i.e. continuous neurogenesis and superior resistance to ischemia (Kojo et al., 2010).

Astrocytes constitute a population of glial cells which participate actively in brain circuitry and processing; furthermore, they are involved in the formation, maturation and elimination of synapses, ionic homeostasis, clearance of neurotransmitters, regulation of extracellular space volume, modulation of synaptic activity and plasticity, as well as rhythm generation and neuronal network patterns (Vasile, Dossi, & Rouach, 2017). Reactive astrogliosis may be elicited by all forms of CNS insults through molecular mediators released by al cell types in CNS tissues (Sofroniew & Vinters, 2010).

The hippocampus is very sensitive to ageing processes: structural and physiologic changes, such as cognitive deficits, neuron loss and an increase in the number of astrocytes are associated with increased age. It has been demonstrated that, in aged, bite-raised SAMP8 mice, the number of astrocytes is significantly increased in the hippocampal regions CA1, CA3 and DG when compared to age-matched controls, indicating an enhancement of the aging process due to the bite-raised condition (Kubo, Saitoh et al., 2008); interestingly, this activation of the microglia was reported in male DDY mice, which do not display the accelerated aging that is the hallmark of SAMP8 mice.

In conclusion, raising the bite has been shown to be associated with a reduction in the number of hippocampal neurons, with suppressed neurogenesis due to a decreased BDNF expression, with increased apoptosis in the DG, with learning and memory deficits and with the activation of glial cells, enhancing the effects of the ageing process; moreover, the extent of the damage was shown to correlate with the duration of the bite-raised condition.

4.2.2. Dendritic spines

Dendritic spines are postsynaptic sites of excitatory input in the mammalian nervous system and, in the hippocampus, they are a source of synaptic contact that may be involved in learning and memory processes (Kubo, Kojo et al., 2008). The bite-raised condition not only

enhanced the age-related decline in spatial learning and the decrease in the number of dendritic spines in the hippocampus, but also induced a decrease in the number of spines in CA1 pyramidal cells in aged mice with a reduced learning ability. It is suggested by the Authors, even though the mechanism of dendritic spine reduction remains unexplained, that the bite raised condition may affect input from the hippocampal CA3 region; as CA1 pyramidal cells receive excitatory inputs from the entorhinal area and from both ipsilateral and contralateral CA3 pyramidal cells, the decreased number of CA1 dendritic spines may be due to a decreased input from CA3 pyramidal cells (Kubo, Kojo et al., 2008). As previously discussed in this review, the bite-raised condition has in fact been shown to be associated with a reduction in the number of hippocampal CA3 pyramidal cells (Kubo et al., 2007), (Kubo, Kojo et al., 2008).

4.3. The bite-raised condition and electromyographical alterations of the masticatory muscles

In the literature reviewed, the bite-raised condition in animal models was accompanied by an altered EMG activity of the masseter and digastric muscles during mastication (Yaffe et al., 1991); (Matsuka et al., 1998); (Kanayama et al., 2011). In the rat, it has been reported that EMG activity in the masseter muscles showed ample fluctuations in the 4 days following the bite-raising procedure; the situation stabilized at day 7, when all the animals showed a significant decrease in masseter EMG activity. In the course of following weeks, masseter EMG activity slowly increased towards control levels; however, the pre-bite-raising procedure EMG activity has not been shown to be regained in the course of the observation, which lasted for 28 days (Yaffe et al., 1991). Interestingly, the EMG activity of the digastric, a jaw depressor muscle, has been shown to be significantly increased in the bite raised condition (Matsuka et al., 1998). On the other hand, a bite raising apparatus positioned on the lower incisors of guinea pigs induced a significant increase in the EMG activity of both the masseter and the digastric muscles (Kanayama et al., 2011). It must be noted, however, that rodent incisor teeth are quite different, both in structure and innervation, when compared to posterior teeth: it is possible that the different EMG alteration observed when rodent incisors are involved in the bite-raising procedure reflects these functional and anatomical characteristics (Piancino et al., 2017). The main limitation of these studies is the short observation time, limited to a few days or weeks. In a clinical setting, where the bite-raising procedure is carried out for orthodontic reasons, the appliances remain in the patient's mouth for variable periods of time. More research is needed to clarify whether, and to what extent, the EMG alterations evolve during this time. The lowering of the EMG activity of the masseter muscle in the bite-raised condition is probably due to the lack of information from the periodontal mechanoreceptors, particularly those associated with molars, that are known to play a primary role in establishing the most energetically convenient and preservative pattern of mandibular movements, especially influencing the power phase of closure (Piancino et al., 2017).

In conclusion, raising the bite has been found to be associated with a reduction in the EMG activity of the masseter muscle, an elevator of the jaw, and an increase in the EMG activity of the digastric muscle, a depressor of the jaw. These alterations tended to lessen with time; however, the return to a normal pattern of masticatory muscles EMG activity in the bite-raised subject has not been reported in any of the articles reviewed.

4.4. Comments

This systematic review was conducted in order to evaluate the bite-raised condition's consequences on the central nervous system, its morphological effects, especially in the region of the hippocampus, the hormonal changes on the hypothalamic-pituitary-adrenal axis, and the behavioral outcomes as have emerged in studies in animals

An important finding of this review is that the results of the articles included are in complete agreement regarding the effects of occlusal disharmony caused by the bite-raised condition on all the topics considered and in different animal models, including mice, rats, rabbits, guinea pigs and primates. The results showed that the bite-raised condition is a cause of stress, accompanied by an increase of plasma corticosterone and of urinary cortisol, and a risk factor for hypersensitivity to novel form of stress. It is associated with a reduction in the number of neurons and synapses and suppressed neurogenesis, it increases the effects of ageing on the hippocampus, leading to memory and learning deficits in aged mice; it is accompanied by the activation of glial cells. Lastly, it interferes with the neuromuscular control of mastication, as it induces a reduction in the electromyographical activity of the masseter muscle and an increase in the EMG activity of the digastric muscle.

Occlusal disharmony is defined by as a phenomenon in which contacts of opposing occlusal surfaces are not in harmony with other tooth contacts and/or the anatomic and physiologic components of the craniomandibular complex; *occlusal stability* is defined as the equalization of contacts that prevents tooth movement after closure (Á, 2005). Occlusal disharmony may be brought about experimentally by means of removal of molar teeth, crown abrasion, raising the bite or positioning a single, asymmetrical obstacle to a balanced pattern of points of contact between the arches. The bite-raised condition is, therefore, a form of clinically induced occlusal disharmony. The bite-raising technique is used by clinicians to position fixed orthodontic appliances in the presence of difficult occlusal conditions (e.g. deep bite) and is therefore widely used in young patients with permanent dentition. It does not have any therapeutic meaning, as it is exclusively a way to avoid technical problems.

The bite-raised condition, like other forms of occlusal disharmony, has been shown to be responsible for acute and chronic stress in animal models, as well as to be a risk factor for hypersensitivity for novel forms of stress. Biochemical studies in primates, rats and mice showed that the bite-raised condition is accompanied by the stimulation of the HPA axis, leading to a rapid incretion of GCs (Budtz-Jørgensen, 1981); (Yoshihara et al., 2001); (Ichihashi et al., 2007); (Iinuma et al., 2008). The stress induced by the bite-raised condition and psychological stress in rats were shown to have synergistical effects on GCs incretion and behavioral test scores (Tang et al., 2017). A sustained stress response was identified in a late-onset but long-lasting incretion of AVP in the hypothalamus. Moreover, the bite-raised condition has been shown to be a risk factor for hypersensitivity to novel forms of stress. Interestingly, the reverse is also true: the masticatory function has been shown to be a stress coping behaviour in rodents and humans, the hormonal mechanisms of which have been recently described (Kubo, Iinuma, & Chen, 2015).

A number of studies including behavioural tests conducted on mice and rats in the bite-raised condition demonstrated that the bite-raised condition induces spatial-orientation deficits in aged SAMP8 mice and that the entity of the deficit is dependent upon the occlusal disharmony's duration. (Kubo et al., 2007); (Kubo, Kojo et al., 2008); (Ichihashi et al., 2007); (Iinuma et al., 2008); (Mori et al., 2013); (Yamada et al., 2013). Even though psychological stress had a greater impact on test scores, the bite-raised condition was shown to negatively impact performance; interestingly, the negative effect of the occlusal disharmony tended to increase with time (Tang et al., 2017).

The bite-raised condition in mice was shown to be associated with a number of different adverse effects in the CNS and especially in the hippocampus: reduction of cell proliferation, differentiation and survival, as well as increased apoptosis, glial cell proliferation and a reduction in the expression of brain-derived neurotrophic factor (Arakawa et al., 2007); (Iinuma et al., 2008); (Kubo et al., 2007), (Kubo, Saitoh et al., 2008); (Kojo et al., 2010); (Mori et al., 2013), (Mori et al., 2016). It was also shown that, in bite-raised mice, the reduced learning ability was associated with a reduction in the number of dendritic spines in hippocampal region of cornu ammonis 1 (CA1)

(Kubo, Kojo et al., 2008). Occlusal disharmony, therefore, appears to enhance the effects of ageing on the hippocampus, a very sensitive structure; again, the extent of the damage correlated with the duration of the bite-raised condition.

Even if no direct evidence of the bite-raised condition as a stressor is available in human subjects, given the level of agreement previously cited among the Authors regarding molecular, histological and behavioural findings in different animal models, the possibility of similar effects in human patients treated with bite-raising appliances should be taken seriously and should be further investigated, especially in the intrinsically stressful condition that is adolescence, the period of life during which bite raising procedures are more commonly employed.

The bite-raising technique is also frequently used to treat adult patients. It is worth mentioning that SAMP8 mice have been used as an animal model for Alzheimer's disease, as they exhibit an accelerated ageing process, a reduced life span and an early cognitive deterioration. It is very likely that the etiological factors of Alzheimer's disease (the main cause of dementia in the western world and a growing public health concern), many of which are still little known, are active years or decades before its clinical manifestation. Moreover, the hippocampus plays a very important role in Alzheimer's disease and other forms of dementia. In the literature reviewed, the bite-raised condition in mice has been shown to accelerate the process of hippocampal ageing, as demonstrated by molecular and histological examination, as well as behavioural tests. More research is needed to clarify whether a similar accelerated ageing of neural structures is precipitated in humans by the bite-raised condition, as it is in rodents; nonetheless, such interesting and noteworthy findings in a mammalian animal model, which is so widely used in medical research to describe and elucidate physio-pathological processes that concern human beings, should at least bring about a cautious attitude towards these clinical procedures. Moreover, a recent systematic review and metanalysis of clinical studies concluded that loss of teeth increases the risk of cognitive impairment and dementia, which is in accord with the demonstration in animal models that masticatory dysfunction caused by molar extraction, occlusal disharmony or soft-diet feeding induces pathological changes in the hippocampus and cerebral cortex, resulting in learning and memory deficit (Cerutti-Kopplin et al., 2016).

Electromyographical alterations were found in rats and rabbits when the bite-raising apparatus was placed in the posterior occlusal region (Yaffe et al., 1991); (Matsuka et al., 1998). The EMG activity of the masseter, a jaw elevator, was found to be reduced and was not shown to return to baseline levels within experimental observation time; the EMG activity of the digastric, a jaw depressor, was found to be increased. If the bite raising appliance was positioned in the incisal region of guinea pigs, the EMG activity of both masseter and digastric appeared to be increased (Kanayama et al., 2011). Even though this review is limited to research conducted on animal models, it is worth mentioning a recently published study (Pativetpinyo, Supronsinchai, & Changsiripun, 2018) in which a group of human volunteers underwent a bite-raising procedure in the posterior occlusal regions, in all respects similar to the normal clinical technique: the EMG activity of the anterior temporalis and masseter muscles was found to be reduced during mastication and forced clench, which is in accord with the results in animal models.

Though extensively used, bite-raising techniques have clearly delineated patho-physiological implications, in animal models, that are not, in general, well known by clinicians: we believe that the decision to opt for such strategies in the course of orthodontic treatments, especially during adolescence, should be accompanied by the awareness of the research results described in this review.

5. Conclusions

The results of this review, with a high level of agreement between Authors and different animal models, indicate the importance of occlusal stability. Occlusal disharmony due to the bite-raised condition has been shown to be a source of stress and to negatively affect the organism's response to stress, the structure of the hippocampus and its role in memory and spatial orientation; furthermore, it has been shown to disturb the electromyographical activity of masticatory muscles. The results of research conducted on animal models, showing stress as well as cognitive and neural alterations extending well beyond the boundaries of the oral cavity, do not necessarily apply directly to human beings. In this context, more clinical research, with special attention to adolescent patients, is necessary to clarify whether, in humans, the bite-raised condition is accompanied by adverse effects comparable to those observed in animals. Nevertheless, on account of the results of this review and of the mounting evidence in favour of a close relationship between the central nervous system and a condition of oral health and occlusal stability, and considering that the most fundamental aspects of the HPA axis are similar across the phylogenetic trajectory from rodents to humans (Azuma et al., 2017), a degree of care should perhaps be exercised when choosing a bite-raising appliance in the clinical setting.

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Declaration of Competing Interest

No conflict of interest.

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References

Á, Á. (2005). The glossary of prosthodontic terms. The Academy of Prosthodontics. *The Journal of Prosthetic Dentistry, 94*(1), 83. https://doi.org/10.1016/0168-8510(94)90003-5.

Arakawa, Y., Ichihashi, Y., Iinuma, M., Tamura, Y., Iwaku, F., & Kubo, K.-Y. (2007). Duration-dependent effects of the bite-raised condition on hippocampal function in SAMP8 mice. *Okajimas Folia Anatomica Japonica, 84*(3), 115–119. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18186225.

Azuma, K., Zhou, Q., Niwa, M., & Kubo, K. (2017). Association between mastication, the Hippocampus, and the HPA Axis: A comprehensive review. *International Journal of Molecular Sciences, 18*(8), 1687. https://doi.org/10.3390/ijms18081687.

Budtz-Jørgensen, E. (1981). Occlusal dysfunction and stress. An experimental study in macaque monkeys. *Journal of Oral Rehabilitation, 8*(1), 1–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6935390.

Cerutti-Kopplin, D., Feine, J., Padilha, D. M., de Souza, R. F., Ahmadi, M., Rompré, P., ... Emami, E. (2016). Tooth loss increases the risk of diminished cognitive function. *JDR Clinical and Translational Research, 1*(1), 10–19. https://doi.org/10.1177/2380084416633102.

Fukushima-Nakayama, Y., Ono, T., Hayashi, M., Inoue, M., Wake, H., Ono, T., & Nakashima, T. (2017). Reduced mastication impairs memory function. *Journal of Dental Research, 96*(9), 1058–1066. https://doi.org/10.1177/0022034517708771.

Ichihashi, Y., Arakawa, Y., Iinuma, M., Tamura, Y., Kubo, K.-Y., Iwaku, F., ... Onozuka, M. (2007). Occlusal disharmony attenuates glucocorticoid negative feedback in aged SAMP8 mice. *Neuroscience Letters, 427*(2), 71–76. https://doi.org/10.1016/j.neulet.2007.09.020.

Ichihashi, Y., Saito, N., Arakawa, Y., Kurata, C., Iinuma, M., Tamura, Y., ... Kubo, K.-Y. (2008). The bite-raised condition in aged SAMP8 mice reduces the expression of glucocorticoid receptors in the dorsal and ventral hippocampus. *Okajimas Folia Anatomica Japonica, 84*(4), 137–142. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18464530.

Iinuma, M., Ichihashi, Y., Hioki, Y., Kurata, C., Tamura, Y., & Kubo, K. (2008). Malocclusion induces chronic stress. *Okajimas Folia Anatomica Japonica, 85*(1), 35–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18833910.

Kanayama, H., Masuda, Y., Adachi, T., Arai, Y., Kato, T., & Morimoto, T. (2011). Alteration of masticatory muscle EMG activities during chewing after a reversible bite-raising in guinea pigs. *Archives of Oral Biology, 56*(8), 793–798. https://doi.org/10.1016/j.archoralbio.2011.01.009.

Katayama, T., Mori, D., Miyake, H., Fujiwara, S., Ono, Y., Takahashi, T., ... Kubo, K.-Y. (2012). Effect of bite-raised condition on the hippocampal cholinergic system of aged SAMP8 mice. *Neuroscience Letters, 520*(1), 77–81. https://doi.org/10.1016/j.neulet.

2012.05.035.
Kojo, A., Yamada, K., Kubo, K., Yamashita, A., & Yamamoto, T. (2010). Occlusal disharmony in mice transiently activates microglia in hippocampal CA1 region but not in dentate gyrus. *The Tohoku Journal of Experimental Medicine, 221*(3), 237–243. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20581431.
Kubo, K., Iinuma, M., & Chen, H. (2015). Mastication as a stress-coping behavior. *BioMed Research International, 2015*, 876409. https://doi.org/10.1155/2015/876409.
Kubo, K., Kojo, A., Yamamoto, T., & Onozuka, M. (2008). The bite-raised condition in aged SAMP8 mice induces dendritic spine changes in the hippocampal region. *Neuroscience Letters, 441*(2), 141–144. https://doi.org/10.1016/j.neulet.2008.05.027.
Kubo, K., Murabayashi, C., Kotachi, M., Suzuki, A., Mori, D., Sato, Y., ... Iinuma, M. (2017). Tooth loss early in life suppresses neurogenesis and synaptophysin expression in the hippocampus and impairs learning in mice. *Archives of Oral Biology, 74*, 21–27. https://doi.org/10.1016/j.archoralbio.2016.11.005.
Kubo, K., Saitoh, N., Kogaya, Y., Iwaku, F., Ichihashi, Y., Arakawa, Y., ... Tamura, Y. (2008). The bite-raised condition enhances the aging process in the dorsal and ventral hippocampus. *Okajimas Folia Anatomica Japonica, 85*(2), 43–48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18975611.
Kubo, K., Yamada, Y., Iinuma, M., Iwaku, F., Tamura, Y., Watanabe, K., ... Onozuka, M. (2007). Occlusal disharmony induces spatial memory impairment and hippocampal neuron degeneration via stress in SAMP8 mice. *Neuroscience Letters, 414*(2), 188–191. https://doi.org/10.1016/j.neulet.2006.12.020.
Matsuka, Y., Kitada, Y., Mitoh, Y., Adachi, A., & Yamashita, A. (1998). Effects of a bite-raising splint on the duration of the chewing cycle and the EMG activities of masticatory muscles during chewing in freely moving rabbits. *Journal of Oral Rehabilitation, 25*(2), 159–165. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9576602.
Miyake, H., Mori, D., Katayama, T., Fujiwara, S., Karasawa, N., Onozuka, M., & Kubo, K. (2011). Effects of occlusal disharmony on activity in the paraventricular nucleus. *Neuroscience Research, 71*, e367. https://doi.org/10.1016/j.neures.2011.07.1612.
Miyake, H., Mori, D., Katayama, T., Fujiwara, S., Sato, Y., Azuma, K., & Kubo, K.-Y. (2016). Novel stress increases hypothalamic-pituitary-adrenal activity in mice with a raised bite. *Archives of Oral Biology, 68*, 55–60. https://doi.org/10.1016/j.archoralbio.2016.03.020.
Mori, D., Katayama, T., Miyake, H., Fujiwara, S., & Kubo, K.-Y. (2013). Occlusal disharmony leads to learning deficits associated with decreased cellular proliferation in the hippocampal dentate gyrus of SAMP8 mice. *Neuroscience Letters, 534*, 228–232. https://doi.org/10.1016/j.neulet.2012.12.004.
Mori, D., Miyake, H., Mizutani, K., Shimpo, K., Sonoda, S., Yamamoto, T., ... Kubo, K. (2016). Effects of occlusal disharmony on the hippocampal dentate gyrus in aged senescence-accelerated mouse prone 8 (SAMP8). *Archives of Oral Biology, 65*, 95–101. https://doi.org/10.1016/j.archoralbio.2016.01.015.
Pativetpinyo, D., Supronsinchai, W., & Changsiripun, C. (2018). Immediate effects of temporary bite-raising with light-cured orthodontic band cement on the electromyographic response of masticatory muscles. *Journal of Applied Oral Science : Revista FOB, 26*(0), e20170214. https://doi.org/10.1590/1678-7757-2017-0214.
Piancino, M. G., Isola, G., Cannavale, R., Cutroneo, G., Vermiglio, G., Bracco, P., & Anastasi, G. P. (2017). From periodontal mechanoreceptors to chewing motor control: A systematic review. *Archives of Oral Biology, 78*, 109–121. https://doi.org/10.1016/j.archoralbio.2017.02.010.
Piancino, M. G., & Kyrkanides, S. (2016). *Understanding masticatory function in unilateral crossbites. Understanding masticatory function in unilateral crossbites.* Wiley Blackwellhttps://doi.org/10.1002/9781118971901.
Sofroniew, M. V., & Vinters, H. V. (2010). Astrocytes: Biology and pathology. *Acta Neuropathologica, 119*(1), 7–35. https://doi.org/10.1007/s00401-009-0619-8.
Tada, A., & Miura, H. (2017). Association between mastication and cognitive status: A systematic review. *Archives of Gerontology and Geriatrics, 70*, 44–53. https://doi.org/10.1016/j.archger.2016.12.006.
Tang, X., Li, J., Jiang, T., Han, S.-H., & Yao, D.-Y. (2017). Experimental occlusal disharmony - A promoting factor for anxiety in rats under chronic psychological stress. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 75*, 165–175. https://doi.org/10.1016/j.pnpbp.2017.02.006.
Vasile, F., Dossi, E., & Rouach, N. (2017). Human astrocytes: Structure and functions in the healthy brain. *Brain Structure & Function, 222*(5), 2017–2029. https://doi.org/10.1007/s00429-017-1383-5.
Wolf, S. A., Boddeke, H. W. G. M., & Kettenmann, H. (2016). Microglia in physiology and disease. *Annual Review of Physiology, 79*(1), 619–643. https://doi.org/10.1146/annurev-physiol-022516-034406.
Yaffe, A., Tal, M., & Ehrlich, J. (1991). Effect of occlusal bite-raising splint on electromyogram, motor unit histochemistry and myoneuronal dimensions in rats. *Journal of Oral Rehabilitation, 18*(4), 343–351. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1832446.
Yamada, K., Ono, Y., Kubo, K., Yamamoto, T., & Onozuka, M. (2013). Occlusal disharmony transiently impairs learning and memory in the mouse by increasing dynorphin a levels in the Amygdala. *The Tohoku Journal of Experimental Medicine, 230*(1), 49–57. https://doi.org/10.1620/tjem.230.49.
Yoshihara, T., Matsumoto, Y., & Ogura, T. (2001). Occlusal disharmony affects plasma corticosterone and hypothalamic noradrenaline release in rats. *Journal of Dental Research, 80*(12), 2089–2092. https://doi.org/10.1177/00220345010800121301.