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From periodontal mechanoreceptors to chewing motor control: A systematic review

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ABSTRACT

Purpose: This critical review summarizes the current knowledge of the structural and functional characteristics of periodontal mechanoreceptors, and understands their role in the signal pathways and functional motor control.
Method: A systematic review of the literature was conducted. Original articles were searched through Pubmed, Cochrane Central database and Embase until january 2016.
Result: 1466 articles were identified through database searching and screened by reviewing the abstracts. 160 full-text were assessed for eligibility, and after 109 exclusion, 51 articles were included in the review process. Studies selected by the review process were mainly divided in studies on animal and studies on humans. Morphological, histological, molecular and electrophysiological studies investigating the periodontal mechanoreceptors in animals and in humans were included, evaluated and described.
Conclusion: Our knowledge of the periodontal mechanoreceptors, let us conclude that they are very refined neural receptors, deeply involved in the activation and coordination of the masticatory muscles during function. Strictly linked to the rigid structure of the teeth, they determine all the functional physiological and pathological processes of the stomatognathic system. The knowledge of their complex features is fundamental for all dental professionists. Further investigations are of utmost importance for guiding the technological advances in the respect of the neural control in the dental field.
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Contents

Abbreviations: MN, mesencephalic nucleus receptors; PGP, Protein Gene Product; TG, trigeminal ganglion.

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1. Introduction

Functional movements of the stomatognathic system and their relative forces depend on signals arising from various sensory organs in the orofacial structures.

A special role is played by periodontal mechanoreceptors and their sensory innervation, located in the periodontal ligament, that is the optimal location for detecting the functional forces on the teeth. They are involved in mechanotransduction and chewing motor control, but there are important limitations of knowledge in the field. For exemple (Piancino & Kyrkanides, 2016), even though mastication is a dynamic process, studies regarding periodontal mechanoreceptors are usually conducted in static conditions and mostly in animals, that are characterized by different teeth and occlusion with respect to the humans, often disregarding the functional differences of teeth.

There are, mainly, two type of studies, hystological and electrophysiological, that are not easy to correlate and without agreement as regards the results.

This article aims to review the progress in the field, especially during the last three years, with a special attention to the functional significance of experimental results.

There have been a number of molecular reports; however, to understand the impact of these reports on the mechanisms of motor control we need to go back to the earliest physiological studies and these are briefly described, commented and integrated with recent molecular data.

The main results of basic research will be summarized in the first part of this review, dividing the animal from the human studies, the second part being dedicated to the signal pathways arising from mechanotransduction.

2. Materials and methods

2.1. Search strategy

A systematic review of the literature was conducted. Original articles were searched through Pubmed, Cochrane Central database and Embase until january 2016.

The research has been done with the following free words: periodontal AND ('mechanoreceptor'/exp OR 'mechanoreceptor'), periodontal mechanorecept* NOT dental implant*, periodontal mechanorecept* AND brain NOT dental implant*; and with the following MESH Terms ("Periodontium/innervation"[MeSH Terms]) AND "Neurons/physiology" [MAJR], periodontal AND mechanoreceptor, (("Mechanoreceptors"[MAJR] AND "Physical Stimulation" [MeSH Terms]) AND "Action Potentials" [MeSH Terms]) AND "Axons" [MeSH Terms]", (("Mechanotransduction, Cellular" [MAJR]) AND"Humans"[MeSH Terms]) AND

"Sensory Receptor Cells" [MAJR], (("Mechanoreceptors*/physiology" [MAJR] AND "Physical Stimulation" [MeSH Terms]) AND "Action Potentials" [MeSH Terms]) AND "Axons/physiology" [MeSH Terms], (("Malocclusion" [MeSH Terms]) AND "Integrins" [MAJR]) AND "Humans" [MeSH Terms], (("Brain Stem"[MAJR]) AND "Face" [MeSH Terms]) AND "Sensory Receptor Cells" [MeSH Terms]", (("Humans" [MeSH Terms]) AND "Feedback, Sensory" [MAJR]) AND"Stomatognathic System" [MeSH Terms]", ("Mastication" [Mesh] AND "Malocclusion" [Mesh]) AND "Electromyography" [Mesh] AND "Humans" [Mesh].

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 were checked by a research librarian. Unpublished studies, gray literature or studies not published in English were excluded.

3. Results

3.1. Search results

1466 articles were identified through database searching and screened by reviewing the abstracts. 160 full-text were assessed for eligibility, and after 109 exclusion, 51 articles were included in the review process as reported in Fig. 1.

3.2. Type of selected studies

Studies selected by the review process were mainly divided in studies on animal (Chen & Wong, 2013; Higuchi et al., 2008; Hitomi et al., 2009; Honma, Kato, Shi, Yatani, & Wakisaka, 2012; Honma, Taki, Lei, Niwa, & Wakisaka, 2010; Iizuka et al., 2009; Jabbar et al., 2007; Korkmaz et al., 2009; Ma, Gao, Fang, & Yang, 2012; Miki et al., 2015; Ohishi et al., 2009; Rahman et al., 2011; Saito et al., 2009; Umemura et al., 2010) and studies on humans(Huang, Corpas, Martens, Jacobs, & Lambrichts, 2011; Kang, Nam, Kim, & Lee, 2010; Tsutsumi et al., 2013; Ziegler et al., 2010) (Table 1). The selection was decided on data reporting, not on study design, due to the variability of the study project, approach and methods. Morphological, histological, molecular and electrophysiological studies investigating the periodontal mechanoreceptors in animals and in humans were included.

4. Studies in animals

4.1. Histological studies in animals

4.1.1. Cytological features and cytochemistry

Periodontal mechanoreceptors are known to be receptors in the periodontal ligament that respond to surprisingly low contact force levels (<1 N) (Newton) applied to the teeth. The functions of nerve fibers in the periodontal ligament, junctional epithelium and gingiva are coordinated with the dental pulp and dentin

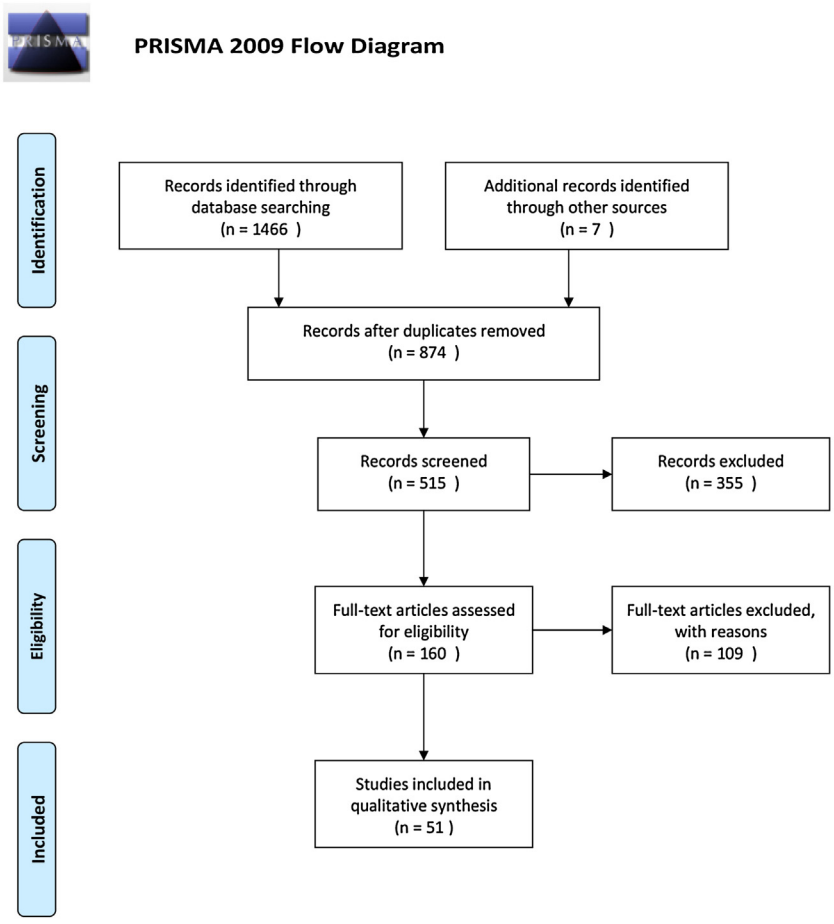

Fig. 1. Flow-chart according to PRISMA statements.

innervation to form an integrated set of sensory systems needed for normal somatosensory reflexes and perception of the external forces on teeth. Their ultrastructural specialization is related to the functional properties of the periodontal innervation (threshold, adaptation etc).

Although various type of mechanoreceptors are present in the periodontal ligament, studies have shown that the Ruffini ending is the primary mechanoreceptor in this location (Byers & Dong, 1989). The Ruffini endings are distributed in specialized compartments of dense connective tissue such as tendons, the fibrous part of joints and ligaments or around hairs (Iggo & Andres, 1982); they have been categorized as a low threshold, stretch mechanoreceptors, slowly-adapting type II (Biemesderfer, Munger, Binck, & Dubner, 1978; Chambers, Andres, von Duering, & Iggo, 1972) and comprise multiple-branching nerve fibers encapsulated in thin connective tissue membranes; the periodontal mechanoreceptors are slowly adapting, direction sensitive, low threshold stretch receptors of Ruffini type. They, usually, do not show any capsule around the endings and are characterized by specialized fingers extending out from the terminals into the extracellular matrix of the ligament; this may offer more rapidly adapting properties in the periodontium than the capsulated cylindrical receptors in the skin (Byers & Dong, 1989; Dong, Shiwaku, Kawakami, & Chudler, 1993; Guven et al., 2014).

The main periodontal Ruffini nerve endings have been classified as type 1 and 2. Type 1 shows lamellar terminal Schwann cells and expanded axon terminals with axonal spines which penetrate surrounding tissue; type 2 is characterized by lesser-branched Ruffini endings with fewer axonal spines, less basal lamina and fewer Schwann cells. Both of these receptor types are present in the periodontal ligament (Maeda, Ochi, Nakakura-Ohshima, Youn, & Wakisaka, 1999) and can be labelled with Protein Gene Product (PGP) 9.5 mainly in the bone related part of the ligament as shown in Fig. 2. The lack of capsule of the periodontal mechanoreceptors is related to their task.

The axonal elements of the periodontal Ruffini endings are characterized by extensive ramifications, filled with a large number of mitochondria. Ultrastructural data analysis identified a specific type of cell organelles called “receptoplasm”, that are special structures in mechanosensitive terminals (Iggo and Andres, 1982). In the axon terminals, this receptoplasm includes smooth endoplasmic reticulum, multivescicular bodies, mitochondria and a reduced incidence of cytoskeletal structures. These organelles are important and are located where the receptive portions of the

Table 1
Characteristics of included studies.

References	Type of study	Subject	Type of structures analyzed	Marker analyzed	Type of analysis	Results
Studies in animals						
Jabbar et al. (2007)	Molecular	Mice	Ruffini endings during development	Neurotrophin	Immunohistochemical analysis, PCR, Quantitative analysis	Is useful for the nerves development
Higuchi et al. (2008)	Molecular	Rat	Transplanted mandibular molar	Avidin-biotin, Pgp 9.5, Periostin	Histological, Electron microscopy-Immunohistochemical analysis	Labelling of all markers
Hitomi et al. (2009)	Molecular	Rat	Mandibular incisors and trigeminal ganglion	ENaCBeta (Sodium Channels)	Immunohistochemical analysis – Immunofluorescence – PCR	Labelling od ENaCBeta in Schwann and Ruffini Endings
Korkmaz et al. (2009)	Molecular	Rat	Molar	ERK (Extracellular kinase)	Immunohistochemical analysis, Immunofluorescence, Biotin peroxidase	Labelling of ERK in periodontal blood vessels and Ruffini Endings
Ohishi et al. (2009)	Molecular	Rat	Mandibular incisors and trigeminal ganglion, Ruffini endings and Schwann cells	Glial neutrotrophic factor (GDNF)	Immunohistochemical analysis – Protein S-100	Increment GDNF during regeneration
Iizuka et al. (2009)	Molecular	Rat	Mandibular incisors and trigeminal ganglion	Caveolin 1–3	Microscopy Immunolelectron analysis, Western Blot	Labelling of Cav 1 in the Schwann Cells and Ruffini Endings
Saito et al. (2009)	Molecular	Rat	Maxillary incisors	Nestin	Immunohistochemical analysis – PCR	Labelling of Nestin in the Ruffini Endings
Honma et al. (2010)	Molecular	Rat	Mandibular incisors and trigeminal ganglion	SNARE e VAMP (Protein receptors)	Immunohistochemical analysis-PCR	Good labelling of SNAP-25 e VAMP
Umemura et al. (2010)	Molecular	Rat	Trigeminal ganglion, incisors and molars	Diameters and shape of the mesencephalic nucleus	Horseradish Peroxidase analysis	Permit to analyse the development of the nerves
Rahman et al. (2011)	Molecular	Mice	Incisors and trigeminal ganglion	ASIC3 (Ionic Channels)	Immunohistochemical analysis – Immunofluorescence – PCR	Labelling of ASIC3 in the nervous fibres
Honma et al. (2012)	Molecular	Rat	Mandibular incisors and trigeminal ganglion	VGluT glutammate	Immunohistochemical analysis – PCR	Good labelling of VgluT 1,2,3
Ma et al. (2012)	Review	–	Ruffini endings, trigeminal ganglion	Acquaporin	–	Presence AQP1 in the Ruffini endings
Chen and Wong (2013)	Review	–	Voltage insensitive cation channels	ASICs	–	Useful for the neurosensory transduction
Miki et al. (2015)	Molecular	Cat	Deciduous and permanent dentition	PGP 9.5	Immunohistochemical analysis – PCR	Identical distribution of periodontal nerve fibers in deciduous and permanent dentition
Studies in humans						
Kang et al. (2010)	Molecular	Human	First premolar extracted for orthodontic reasons PDL cell in colture	FAK focal adhesion kinase	Elisa, Western Blot, PCR	Upregulation of matrix metalloproteinases and focal adhesion kinase during in vitro mechanical strain
Ziegler et al. (2010)	Molecular	Human	PDL cells during mechanical strain	Map kinases, Metalloproteinases (MMP), Focal Adhesion Kinases	Western blot (WB) analysis and/or indirect immunofluorescence	Mechanical strain modulates the amount of the MMP and the signal transducing molecules
Huang et al. (2011)	Molecular	Human cadaver	Lower canine	Myelinic fibres and Schwann cells	Histological and Immunohistochemical analysis	Concentration of mielinic fibres of 0.3 and 1.3 mm at the root apex
Kim et al. (2013)	Molecular	Human	First premolar extracted for orthodontic reasons PDL cell in colture	Integrin-FAK pathway	PCR, Elisa	Regulation of compressive stress-induced expression of M-CSF, TNF-a, RANKL and OPG and mechanoreceptor function

nerve fiber occur. The receptoplasm can be labelled by different cytochemical biological markers such as Caveolin, (PGP) 9.5 (Iizuka et al., 2009), growth-associated proteins (GAP 43, which are expressed particularly during the regeneration of the axon and Schwann cells) (Wakisaka, Atsumi, Youn, & Maeda, 2000), calretinin, neurotrophin 75, acid phosphatase and cytochrome oxidase enzyme activity, which were found mainly in the mitochondria of the receptor. The amount of receptoplasm is higher in the periodontal Ruffini endings receptors than in the high threshold nociceptors (Byers, 1985).

The fibers are associated with Schwann cells (termed lamellar or terminal Schwann cells) which possess kidney-shaped nuclei (K-cells) and share many ultrastructural features with support cells of other mechanoreceptive terminals such as Meissner or Pacinian corpuscles. The characteristics of the Schwann cells and their relative adjacent nerve fibres, is fundamental to understanding the behaviour of periodontal Ruffini mechanoreceptors. The fact that some biological markers (P75 neurotrophin receptor, growth associated protein GAP-43) showed intense immunoreactivity of the Schwann lamellae around the Ruffini mechanoreceptor, whereas the thin nociceptive-like fibers showed intense axonal staining, suggests that development responses of the periodontal Ruffini mechanoreceptors depend on molecular mechanisms located in Schwann lamellae and not on axonal mechanisms (Byers, 1985).

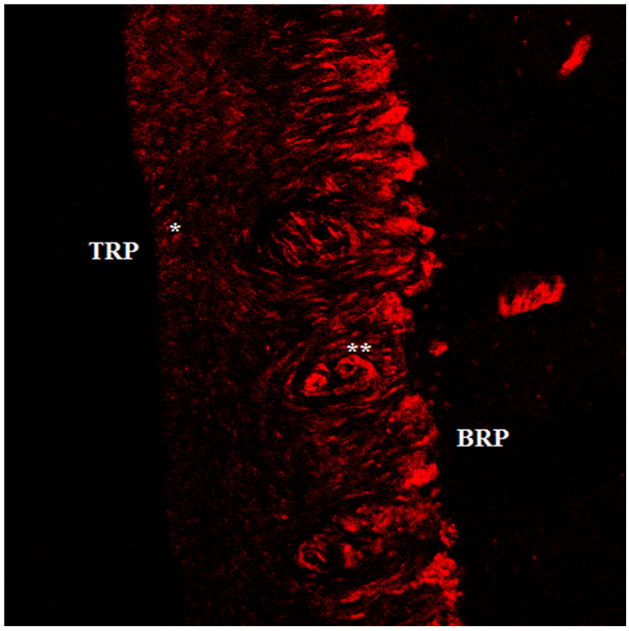

Fig. 2. Immunofluorescence reaction for PGP 9.5 in the periodontal ligament of maxillary rat incisor. It is possible to observe a low PGP 9.5 immunostainig (red fluorescence) in tooth related part (TRP), where it marks thin lines of nervous fibers (*); instead, in bone related part (BRP), it is possible to observe a high PGP 9.5 immunofluorescence pattern which marks, prevalently, receptorial endings of nervous fibers (**). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The periodontal Ruffini ending has been reported to develop a caveola-like structure on the cell membrane of both the axon terminals and Schwann sheaths. Experiments on rat incisors with caveolin-1, −3 (Cav-1, Cav-3) and Ca^{2+}-ATPase showed that Cav-1/Ca^{2+}-ATPase might be involved in the quick elimination of intracellular Ca^{2+} in mechanotransduction (Iizuka et al., 2009). Recently, a number of molecular studies regarding various substances usually found in the central nervous system, have been classified describing the results in Table 1.

Finally, recent studies considered the periodontal ligament as a source of mesenchymal-like stem cells (MSCs). As adequate vascularization and innervation are essential components for

the viability of regenerated tissues, it has been shown that preconditioning with deferoxamine (DFX) and/or fibroblast growth factor-2 (FGF-2) significantly improves the angiogenic secretome of periodontal ligament stem cells (PDLSCs), in particular vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) secretion. However,the data suggest that VEGF is not the only player when it comes to influencing endothelial behavior by the periodontal ligament stem cells. In addition to their plastic adherence and characteristic expression of surface markers (such as CD73, CD90, and CD105, they also display a negative expression of CD14, CD34, and CD45) they are capable of osteogenic, chondrogenic, and adipogenic differentiation.

Together with the periodontal ligament, that is a specialized connective tissue, not only attaching the tooth to the alveolar bone but also performing a sensory function, other stem cell populations derived from the tooth have been investigated, such as the dental pulp population both from the deciduos and permanenet teeth, the apical papilla population at the apex of the developing permanent tooth and the dental follicle population. Those populations are easily accessible and have been named dental stem cells. Different studies support the angiogenic, neuroprotective, and neurotrophic effects of the dental stem cells secretome. Together with their ability to differentiate into endothelial cells and neural cell types, this makes dental stem cells suitable candidates for dental tissue engineering and nerve injury repair (Ratajczak, Bronckaers et al., 2016; Ratajczak, Hilkens et al., 2016).

4.1.2. Receptor location

Periodontal mechanoreceptors are concentrated in the alveolus-related part of the ligament (Ochi, Wakisaka, Youn, Hanada, & Maeda, 1997), in the regions subjected to stretch during tooth use (Fig. 2); their location can change during development and aging. Different type of teeth show different distribution of receptors depending on tooth shape and function. The study of Miki et al. (2015) indicate that the distribution of periodontal nerve fibers in deciduous dentition is almost identical to that in permanent dentition although the number of periodontal nerve fibers in deciduous dentition is low. The sparse distribution of periodontal nerve fibers in deciduous dentition agrees with clinical evidence that children are less sensitive to tooth stimulation than adults. Ruffini mechanoreceptors are contained in the interdental ligaments, being, likely, also involved in detecting movements of one tooth relative to another (Byers, 1985). The mechanoreceptors arborize primarily in the dense portion of the ligament, less in loose perivascular region, and the largest endings occur near the apex of the root for most teeth, but on lingual side of rodent incisors (continuously erupting teeth) (Iggo & Andres, 1982).

4.2. Electrophysiological studies in animals: are the results in agreement with the histological ones?

The mechanoreceptors have been studied not only from an histological point of view, but with electrophysiological experiments also.

Linden and Scott (Linden & Scott, 1989), with electrophysiological studies on cats mandibular canine, located the trigeminal mesencephalic nucleus receptors (MN) near by the fulcrum of the root and the trigeminal ganglion receptors (TG) at the apex and periapical region of the tooth. These results are in disagreements with the histological studies previously described.

The mechanoreceptors have been classified in Slowly and Rapidly adapting receptors, but they are not clearly related to a specific type of nerve ending. A type 3 ending with coiled form (similar to rapidly adapting Meissner corpuscle) may represent a rapidly adapting form. The cutaneous Ruffini endings are of slowly adaptive type only. From the functional data of Cash and Linden, the most slowly adapting receptors appeared located at the apex of the tooth, while the rapidly adapting receptors were located close to the fulcrum of the tooth (Cash & Linden, 1982), but the authors suggest that there might be only one type of periodontal mechanoreceptor adapting to the different functional demands. The issue is still not clear, because the results are deductive and not confirmed by histological evaluation.

4.2.1. Threshold and receptive fields

From animal studies, the threshold sufficient to evoke a response from the majority of the slowly adapting units, resulted between 0.01 and 0.05 N (Cash & Linden, 1982; Nagata et al., 2008). Displacements of the tooth in the order of 2–3 μm would seem to be enough to evoke a response in single neurons. A critical amount of the stimulus is necessary to elicit a response from the rapidly adapting unit, and the latency of response decreases as the application of the stimulus is increased.

The mechanoreceptors are very sensitive to the stimulus direction. The optimal stimulus directions of the incisor-sensitive neurons of rats are oriented labio-lingually or linguo-labially (Tabata & Hayashi, 1994). Subsequent electrophysiological studies on the trigeminal ganglion of rats have shown that in the maxillary molar-sensitive units, the orientation of the predominant optimal

stimulus direction was linguo-buccal or bucco-lingual. In the mandibular molar-sensitive units, the optimal stimulus direction was linguo-buccal, and the units were excited by stimulation of the buccal cusp. Interestingly, the optimal directions are those useful in chewing food (Tabata, Takahashi, & Hayashi, 2006).

Regarding slow and rapid receptors the same authors showed that they are differently located in upper and lower molars, the rapid receptors being more represented in the mandibular teeth that convey the informations from the mandible, i.e. the moving bone, and the slow adapting in the maxillary molars (Fig. 4). The differentiation between upper and lower, anterior and posterior teeth is important for their different functional role (Tabata et al., 2006).

Also, changes during development and load response reflect the strict relationship between function and periodontal mechanoreceptors (see Appendix A).

5. Studies in humans: what do we really know?

5.1. Histological studies

The studies in humans regarding the macroscopic anatomy are few and limited, due to the difficult isolation of the integral human PDL (Table 1). Huang (Fig. 3) studied the human PDL in the lower canine of a cadaver and he found dense innervations by myelinated nerve fibres in close proximity to collagen fibres and alveolar bone and a more densely innervation in the apical as well as mesial and buccal sites of the human canine (Huang et al., 2011).

Some recent studies have been conducted on periodontal ligament (PDL) fibroblasts derived from the ligament tissues of periodontally healthy, non-carious human premolar teeth, extracted for orthodontic reasons. The results showed that the transduction of mechanical stimuli (compressive stimulation) in human PDL cells involves the focal adhesion kinase (FAK) pathway, and the integrin-FAK complex that play a role as a mechanoreceptor in PDL cells. Also, in the light of the findings elaborated from the protein and gene transcription analyses on periodontal ligament fibroblasts subjected to mechanical strain, it has been shown that it involves abundance and activity of FAK/p125FAK –mediated mechanotransduction and identifies activated states of mitogen activated protein (MAP)-kinases, p42/44, extracellular-signal regulated kinase (ERK) and p38-stress kinase as a mechanism for matrix metalloproteinase (MMP)-13 and integrin subunits β1, β3 expression. This may indicate the mechanistic contribution of mechano-transducing molecules on executioners of extracellular matrix homeostasis (Kang et al., 2010; Kim, Park, Park, Lee, & Kang, 2013; Ziegler et al., 2010).

5.2. Electrophysiological studies

The studies on human subjects are mainly electrophysiological; unfortunately, these studies are generally limited and often deductive. In humans the limitation are even greater than animals.

Interestingly, a recent study on human incisors demonstrated the down-regulation of the threshold for perception of force of the receptors during jaw-closing movements (Sowman, Ogston, & Turker, 2007). This study represents an interesting evolution towards dynamic conditions, even though there are still limitations such as the impossibility to reproduce natural chewing cycles, the invasiveness of the device, the forced position of the head of the subject etc.).

From an electrophysiological point of view, the periodontal mechanoreceptors in humans appear to be almost entirely of the slowly adapting type; these units respond with increasing action potential frequencies to increasing magnitudes of stimulation and more than 40–50% of the receptors are spontaneously active, producing action potential in the absence of any applied load. Other studies showed that receptors are located usually around the circumference of the tooth and that they are highly concentrated in the more loaded areas, especially in the distal-lingual direction (Trulsson, 2007).

5.2.1. Threshold and receptive fields

The mechanoreceptors are directionally sensitive. In humans, when a force is applied on the tooth in one direction, the periodontal mechanoreceptors respond with four or six different

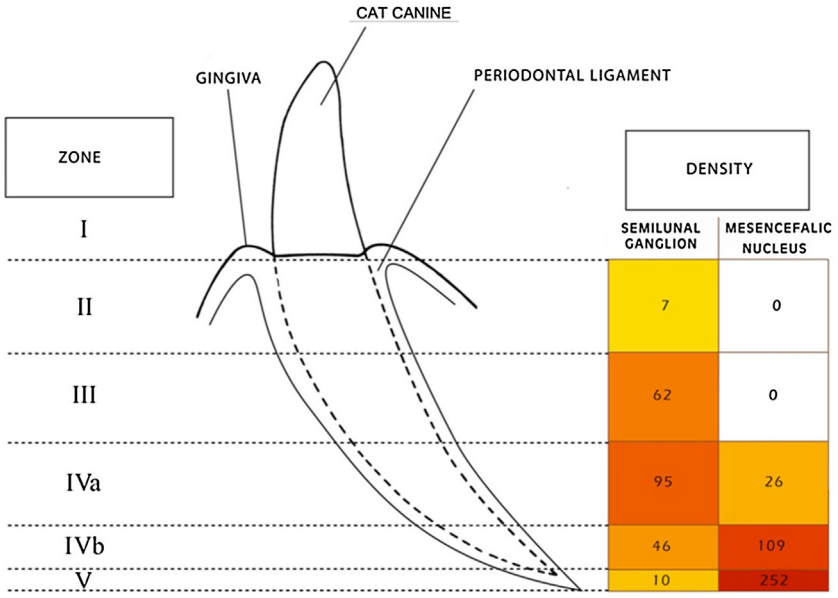

Fig. 3. The image shows the distribution in the lower cat's canine of nerve endings of primary afferent neurons from the trigeminal ganglion (more concentrated in the periapical zone) and from the mesencefalis nucleus (more concentrated in the apical zone) of the lower canine of cats. The diagram is based on the morphological quantitation of Byers and Dong (Byers & Dong, 1989).

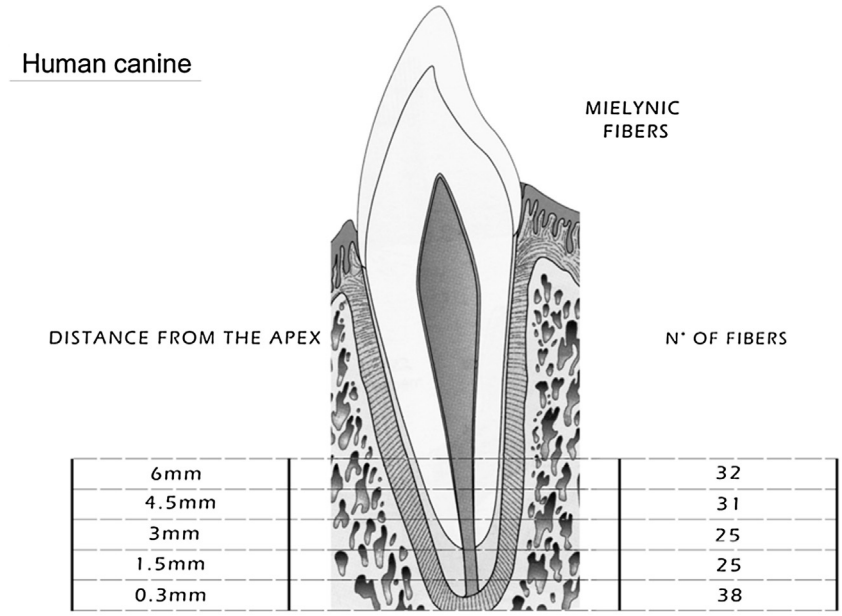

Fig. 4. Average density of myelinated axons in the different portions of the human cadaver canine (Huang et al., 2011). The average density of myelinated nerve fibres increases closer to the apex; the highest density of myelinated structure resulted at the apical level, while the smallest value occurred at the middle level of the root. However, the average diameter did not show any significant differences amongst the different root levels.

afferents, but maximal activation occurs in the direction of the stimulus.

About half of the human periodontal mechanoreceptors respond to a loading of groups of adjacent teeth, typically two or four. However, the existence of multiple tooth receptive fields does not reduce the capability of the central nervous system to locate with precision the force stimulus from a specific tooth. Trulsson showed an high firing rates for bucco-lingual directions, suggesting that the mechanoreceptors are deeply involved in food manipulation (Trulsson, 2007).

Moreover, periodontal afferents, seem to show a tendency to saturate. With regard to the threshold of perception of the force able to activate the receptor, the mean level detected in humans was below 1 N (Johnsen, Svensson, & Trulsson, 2007), but the force rate necessary to split a peanut differs according to the type of teeth involved, increasing distally along the dental arch with an average of 0.60 N for the incisor, 0.77 N for the canine, 1.15 N for the 2nd premolar and 1.74 N for the 1st molar. Trulsson (Trulsson, 2007) also showed that during periodontal anesthesia the magnitude and variability of the hold forces increases for all types of teeth by at least a factor of 2. In subjects with implant-supported prosthesis evidence was found of an impaired adaptation of the muscle activity to food hardness during mastication. Also, significant data showing higher biting and food holding forces of patients with fixed dental prostheses on natural teeth and with implant prostheses, in comparison with subjects with natural teeth, were reported (Lobbezoo et al., 2002; Svensson & Trulsson, 2011). In these subjects, the optimum restoration design is fundamental (Klineberg, Trulsson, & Murray, 2012).

Interestingly, some studies evaluated the "osteoperception", that is an associated mechanosensibility with osteointegrated implant rehabilitation. They have shown a higher tactile sensibility of implant-supported restoration with respect to soft tissue-supported restoration (Ramieri et al., 2004) and an increase in the tactile perception capability of osseointegrated implants over time. Also, tactile perception was found to depend on the implant surface structure and might point to receptors near the implants as the anatomical basis of osseoperception. A contribution to oral kinesthetic perception could come from the activation of possibly periosteal and/or mucosal receptors in the vicinity of the implant fixture, and/or of mucosal receptors beneath the complete denture. Some studies reported that the disruption after surgical mucoperiosteal procedures of Pacinian corpuscoles and free nerve endings involved in the periosteal innervation sensitive to stretching, may be responsible of the reduced directional sensitivity, increasing the validity of the surgical procedures that preserve receptors as much as possible; moreover, other works showed the potential of nerve growth factor (NGF) in accelerating bone healing and improving osseointegration of the implant. Nerve fibers become abundant around the bone/implant interface as the process of osseointegration progresses. With the loss of teeth and periodontal structure, other peripheral receptors dominate and transmit the afferent projections to the sensorimotor cortex and compensate by providing stimulations to the area of bone-anchored implant restorations, but further research is required to understand the important phenomena of osseoperception in order to guide the design of optimized dental implant able to obtain better masticatory results (Mishra, Chowdhary, Chrcanovic, & Branemark, 2016).

6. Central connections of the trigeminal primary afferent neurons: is there a bias?

Understanding the signal pathways arising from periodontal mechanoreceptors is important for the comprehension of the mechanisms that control the masticatory forces. For this reason, special attention has been dedicated to review the literature regarding the central connections of the afferent neurons of periodontal mechanoreceptors. In particular, studies regarding the location of the cell body of the primary afferent that conveys information from the mechanoreceptor to the central nervous system are examined in this section.

The cell bodies of the primary afferent neurons that respond to forces applied to the teeth has been detected in two distinct anatomical sites: the trigeminal ganglion (TG) and the trigeminal mesencephalic nucleus (MN) (Byers & Dong, 1989). Interestingly, specific antibodies can be selective for TG compared to MN neurons (Byers, 1985).

6.1. Primary afferent neurons to TG and to MN

The afferences to the TG have been reported quantitatively greater in the teeth of different animals (Cats, dogs, rats, rabbits and monkeys) (Byers, 1985; Nagata et al., 2008; Tabata, Yamaki, Takahashi, & Hayashi, 2002), with respect to the MN ones, except for the cat canine that is characterized by a majority of afferences to the MN. Byers and Dong (Byers & Dong, 1989) did the morphological quantitation on the cat's canine of the TG endings with respect to the MN ones showing that each type of innervation could be found on all sides of the tooth and that the MN endings are more concentrated in the apical zone of the root, while the TG ones are located in the periapical area, immediately below (Fig. 5).

In rats, the sensory TG nerve endings of molars are five times more numerous at periapical level (immediately under the apex) while the innervation of incisors, in the same animal, resulted concentrated on the lingual side of the tooth, characterized by large mechanoreceptors (Chambers et al., 1972). In rats, the afferences to the TG convey a majority of slowly adapting units, single tooth-sensitive, characterized by a lower touch threshold with respect to the afferents located in the MN (1.8–6.0 g vs 0.5–1.0 g) (Byers, 1985), and a directional sensitivity to touch pressure of tooth displacement.

The neural pathway of the afferents through the TG leads to conscious sensations via the thalamus and cortex integration (Fig. 6).

The mesencephalic nucleus has been considered unique as it contains the only known group of primary afferent neurons from peripheral receptors (Aigouy, Pajot, Raboisson, Vassel, & Woda, 1988; Byers & Dong, 1989; Cash & Linden, 1982; Linden & Scott, 1989; Nagata et al., 2008). The majority of the neurons recorded in the MN are characterized by receptive fields limited to only one tooth and the teeth do not appear equally represented. The cat's canine teeth seem to have the largest representation (Linden & Scott, 1989). The neural pathways of the afferents through the MN leads to unconscious reflexes via the cerebellum (Fig. 6).

The cat's canine needs a special consideration because it has a special functional role that is the killing of the prey: it is used to disarticulate the neck bones and to cut the spinal cord of the prey, which will immediately die. The ability of felines to dislocate the cervical bones is innate and phylogenetically inherited (Leyhausen, 1982). This may explain why the afferent neurons of periodontal mechanoreceptors of a cat's canine are clearly and abundantly located in the mesencephalic nucleus; it is intriguing to hypothesize that they might be considered as proprioceptive afferents, (like muscle spindle), connected to pathways leading to unconscious reflexes involved in mandibular control (via the cerebellum). For this reason, studies on the cat's canine should be interpreted in the light of these ethological considerations.

7. From mechanotransduction to signal pathways: the role of periodontal mechanoreceptors on the chewing pattern motor control

7.1. Sensory feed-back to the rhythmic pattern generator

Recent research has underlined the significance of feed-back from periodontal input to the central pattern generator in the brainstem, during chewing (Morquette et al., 2012). The afferent neurons in the trigeminal ganglion are active during mastication, when using the molar teeth (Figs. 6–7), especially during the power phase of closure, and are sensitive to the force (or to changes of force) applied to the tooth. A model has recently been proposed in which sensory feedback might be responsible for the regulation, through astrocyte activation, of the bursting pattern and frequency of the rhythm generator population of the central pattern generator (Morquette et al., 2012).

Peripheral and cortical inputs from the cortical masticatory area contribute, synergistically, to a more efficient astrocytic activation, decreasing the extracellular Ca^{2+} and enhancing the sodium current. This could, momentarily, turn the population of neurons into the rhythm generator's driving premotoneurons or motoneurons directly. The bursting pattern and frequency of this population could be adjusted by sensory feedback since sensory fibers provide depolarizing inputs activating the bursting neurons (Morquette et al., 2012) (Fig. 6).

The powerful influence of the periodontal mechanoreceptors on the central pattern generator has been clearly demonstrated in

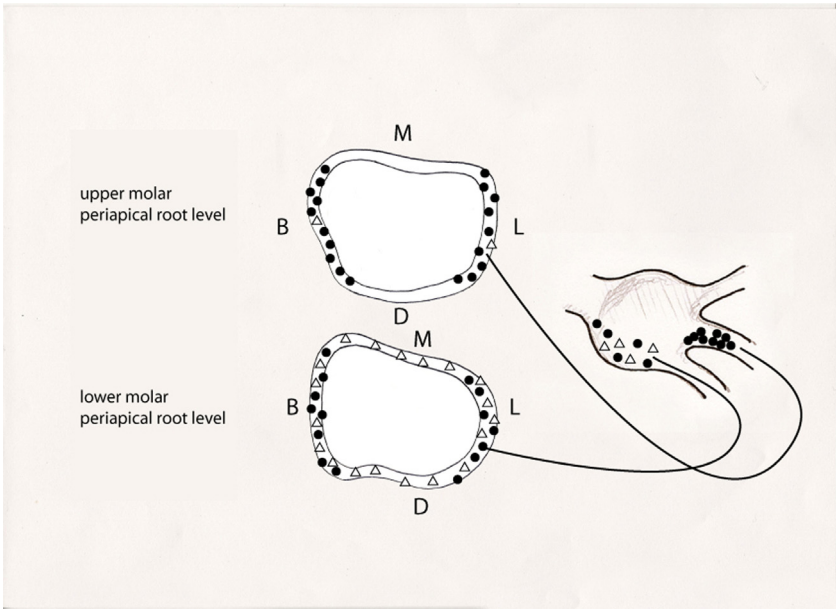

Fig. 5. Different distribution of the upper and lower molar periodontal machanoreceptors in experimental studies in rats. Interestingly the rapid-adapting receptors (white triangles) are more concentrated in the lower molars conveying informations from the moving bone, while slow-adapting receptors (black dots) resulted more concentrated in the maxillary molars.

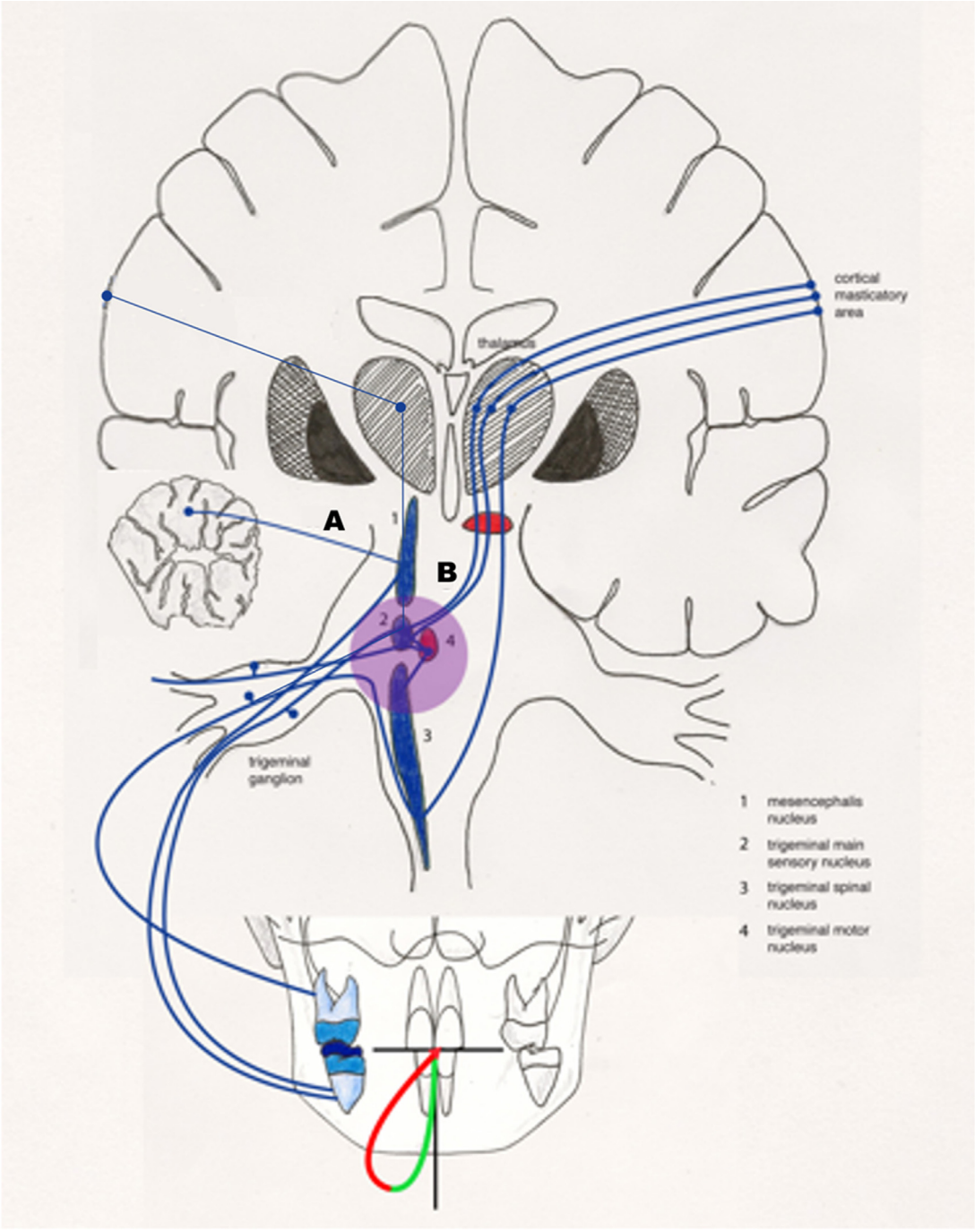

Fig. 6. The pathway of the sensory inputs arising from periodontal mechanoreceptors to the central nervous system is represented. A: pathways of the primary afferent neurons located in the mesencephalic nucleus leading to unconscious reflexes via the cerebellum; this type of neurons are quantitatively represented in the cat's canine; in the other animals they are quantitatively less represented; B: pathways of the primary afferents located in the trigeminal ganglion (the majority) leading to conscious sensation, via the thalamus, to the cortical masticatory area. The sensory inputs from the periodontal mechanoreceptors are very powerful in continuously adapting the chewing pattern to the bolus hardness thanks to the direct connections between the second order neurons to the trigeminal main sensory and spinal nucleus and the central pattern generator (red nucleus in violet area). It has been suggested that inputs from mechanoreceptors might be responsible for the regulation, involving the bursting pattern (violet area) and frequency of the rhythm generator population of the central pattern generator (red nucleus) (Morquette et al., 2012). The pathway of the sensory inputs from periodontal mechanoceptors is bilateral. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

experimental (Lund & Kolta, 2006) and may explain the so-called "reverse sequencing chewing cycles" that have been shown, with high prevalence, in posterior unilateral crossbite patients, during chewing on the crossbite side (Piancino, Bracco, Vallelonga, Merlo, & Farina, 2008; Piancino et al., 2012, 2006, 2016) (Fig. 7). This is consistent with the location and characteristics of periodontal mechanoreceptors, whose inputs contribute to establishing the most energetically convenient and preservative pattern, especially influencing the power phase of closure. As posterior crossbite is characterized by a reverse molar cusp relationship, masticatory function results in "reverse chewing pattern" (reverse direction of closure), thus ensuring the overlap of opposing dental occlusal surfaces. There is evidence that the muscular activation output and coordination during reverse-chewing is altered, as the electromyographic amplitude of the masseter of the crossbite side is significantly lower than the contralateral masseter (Piancino,

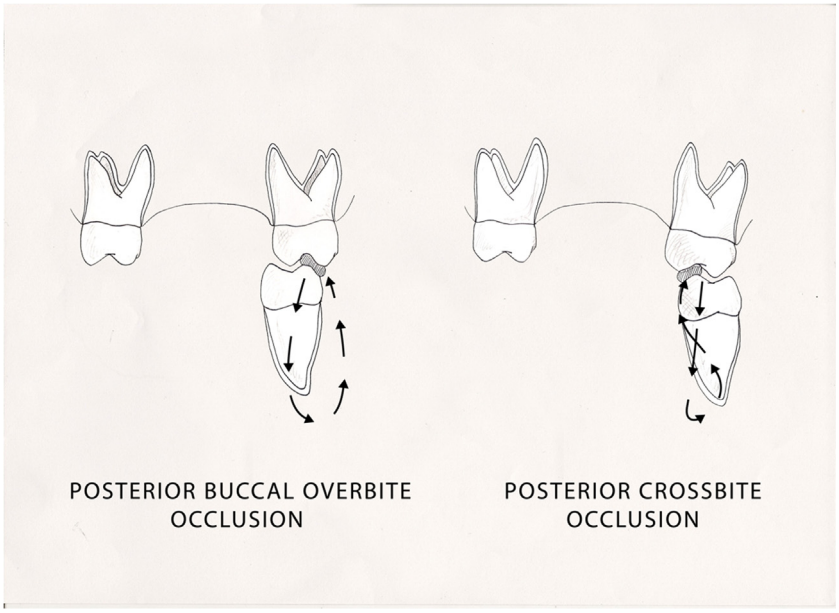

Fig. 7. The image represents the chewing pattern, in the frontal plane, of patients with posterior buccal overbite occlusion and with posterior unilateral crossbite malocclusion involving molar teeth. Considering the powerful influence of periodontal mechanoreceptors on the masticatory motor control of the central pattern generator, the adaptation of the power phase of closure to the posterior occlusion, or malocclusion, is evident. In posterior overbite occlusion, the mandible deviates laterally, towards the bolus side, and then, during closure, medially, through the *trans*-cuspal and intercuspal phases of mastication. In posterior crossbite malocclusion, it is well established an increased frequency of "reverse chewing patterns" during chewing on the affected side, meaning that the mandible, during closure, first deviates medially and then laterally, thus ensuring overlap of opposing dental occlusal surfaces. There is evidence that the muscular activation output and coordination, during chewing on the crossbite side, is altered, being the electromyographic amplitude of the masseter of the crossbite side, significantly lower than the contralateral (Piancino et al., 2009; Piancino et al., 2006).

Farina, Talpone, Merlo, & Bracco, 2009). Based on these results and on the fact that integrins are heterodimeric cell surface membrane proteins linking the extracellular matrix to actin providing bidirectional signaling between the extracellular matrix and the cytoplasm, a biomolecular study evaluating muscle-specific integrins in masseter specimens of patients with severe posterior unilateral crossbite, undergoing orthognathic surgery, was planned. The results showed that the expression of integrins was altered, being significantly lower in the crossbite side muscle than the normal side. Moreover, the integrin β1A (development integrin usually not detectable in adult limb muscles) was clearly detectable in the adult masseter. This means that integrins, in the masseter muscle, are able to play a key role in regulating functional activity, optimizing contractile force (Cutroneo et al., 2012).

7.2. From the trigeminal ganglion to the thalamus

The TG ganglion shows an organized distribution of the afferent neurons: Nagata et al. (Nagata et al., 2008) recorded the discharges of the PMN from the upper incisor and upper molar units in the rostromedial area of the trigeminal ganglion in rabbits, while the lower incisor and lower molar units were distributed in the caudolateral area. The mechanosensitive afferent fibres of the TG connect with second order neurons located in the principal and spinal divisions of the trigeminal sensory nucleus. From there, the information is relayed at the brainstem, to influence the trigeminal motoneurons reflexly, or at the ventrobasal nuclei of the thalamus, and, from there, to the cortical masticatory area (Morquette et al., 2012). Responses from thalamic periodontal mechanoreceptors neurons were also found in rats by Tabata et al. (2002).

7.3. Somatosensory cortex and central projections to the nervous systems

Periodontal sensory information is finally projected to the primary somatosensory cortex (Linden & Scott, 1989). The inputs in the trigeminal nuclei are mapped tooth by tooth, but the projection from the thalamus to the cortex generates a less detailed cortical map, and results in a representation by half arches rather than tooth by tooth. The output of the cortex seems to be important in initiating and coordinating the masticatory movement and for adapting it to the hardness of the bolus (Morquette et al., 2012). Itoh, Nishiura, Tabata, & Watanabe (2002) found a majority of lower incisor-sensitive neurons in the rostromedial area, while neurons of the molar and incisor (especially upper) teeth were found in the rostrolateral area of the cortex.

Interestingly, recent studies aimed to detect the lateralization of the motor control. In experiments on cats, Nishiura et al. (Nishiura, Tabata, & Watanabe, 2000) detected slowly adapting neurons with ipsilateral or contralateral receptive fields in the same somatosensory cerebral hemisphere, as opposed to rapidly adapting neurons, which predominantly received contralateral sensory input. Similar results were shown for mice (Erzurumlu, Murakami, & Rijli, 2010).

Many subcortical areas (amygdala, hypothalamus, anterior pretectal nucleus, periacqueductal grey, raphe nuclei, cerebellum, basal ganglia) are known to project to the trigeminal complex.

Recently, an fMRI (functional magnetic resonance imaging) experiment performed in human subjects by 3T scan showed a bilateral activation of the postcentral gyrus (S1) and parietal operculum (S2) after tactile stimulation of the central maxillary incisors and canine (Habre-Hallage et al., 2014).

8. Future directions

The actual knowledge of the periodontal mechanoreceptors let us conclude that they are very refined neural receptors deeply involved in the activation and coordination of the masticatory muscles. Strictly linked to the rigid structure of the teeth, they determine all the functional physiological and pathological processes of the stomatognathic system, playing an important role in the sensorimotor cortical processes both adaptive and compensatory. The knowledge of their complex features is

fundamental for all dental professionists. Further investigations are of utmost importance to establish a deeper understanding of these phenomena, for improving therapies and guiding technological advances in the respect of the neural control in the dental field. This is the reason why, at the current state of knowledge, a close collaboration between clinicians and researchers is primary.

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Conflict of interests

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Appendix A.

(a) Changes during development

One of the greatest changes during development in the stomatognathic system is the functional conversion of feeding behaviour from sucking to chewing (Barlow, 2009). Since functional conversion is related to the development and maturation of the peripheral nervous system a number of interesting developmental studies demonstrated that the morpho-physiological maturation of periodontal Ruffini endings is closely related to the tooth eruption (Asahito, Ohshima, Hanada, Wakisaka, & Maeda, 1999) and that the final arborization of the Ruffini endings, of axonal spines and thickening of basement membrane are completed shortly after the beginning of the rat incisors (Hayashi et al., 2000; Nakakura-Ohshima, Maeda, Ohshima, Noda, & Takano, 1995) or molar function (Umemura et al., 2010). Interestingly, in the last study, no difference was shown for the neurons conveying the inputs of the muscle spindle of the masticatory muscles, after tooth eruption. This is due to the fact that these neurons have been active since the embryonic period, as swallowing starts in utero.

Various studies have shown that multiple neurotrophins, such as glial cell line-derived neurotrophic factor (GDNF), and Schwann cells are fundamental and stage-specific for the maturation and maintenance of the periodontal Ruffini endings. This neurotrophins are also important neurotrophins because mediates trophic effects on neuronal survival, growth, and target innervation (Hayashi et al., 2000; Hoshino et al., 2003; Igarashi et al., 2007; Maruyama et al., 2005; Ohishi et al., 2009).

(b) Load response

Periodontal mechanoreceptors are directly involved in the response to occlusal load.

Sodeyama et al. (Sodeyama, Maeda, Takano, & Hara, 1996) demonstrated on rats, with different occlusal forces, that occlusal trauma induces specific changes in the distribution and shape of nerve terminals in the periodontal ligament; other studies on rats showed that an improper occlusal force reversibly alters both the axon terminals (Shi, Atsumi, Kodama, Honma, & Wakisaka, 2006) and the functional properties of the periodontal Ruffini endings (Asano, Zeredo, Toda, & Soma, 2007).

(c) Functional Characteristic of Periodontal mechanoreceptor

The results of many studies in human and animals, recording the electrophysiological activity from periodontal mechanoreceptors, have demonstrated the presence of two basic receptor types, both of which respond to the movements of the teeth following the application of an external force. One type is called rapid adapting unit: it generates a transient discharges to a sustained stimulus, and the number of impulses produced is dependent on the rate of application of the stimulus; at faster application rates, more neural impulses are produced. Thus, they are sensitive to both the rate and magnitude of the applied load, but respond only when the load is being applied (Hannam, 1970).

The other type is the slowly adapting unit that, unlike the other different type of unit, continues to generate nerve impulses for longer periods, throughout the tooth displacement and even though the load is no more applied on the tooth. In these types of receptors, the frequency of the impulse during the initiation of the response increases with an increase of the stimulus application; the initial and final frequencies are also dependent on the magnitude of the applied load (Hannam, 1970; Trulsson & Essick, 2010).

References

Aigouy, L., Pajot, J., Raboisson, P., Vassel, A., & Woda, A. (1988). Localisation of the first-order neurone of the jaw opening reflex elicited by periodontal stimulation. *Brain Research*, *473*(2), 380–384.

Asahito, T., Ohshima, H., Hanada, K., Wakisaka, S., & Maeda, T. (1999). Postnatal expression of calretinin-immunoreactivity in periodontal Ruffini endings in the rat incisor: A comparison with protein gene product 9.5 (PGP 9.5)-immunoreactivity. *Archives of Histology and Cytology*, *62*(1), 57–69.

Asano, T., Zeredo, J. L., Toda, K., & Soma, K. (2007). Periodontal masseteric reflex is changed by periodontal sensory modification during occlusal hypofunction in rats. *Journal of Medical and Dental Sciences*, *54*(1), 31–37.

Barlow, S. M. (2009). Central pattern generation involved in oral and respiratory control for feeding in the term infant. *Current Opinion in Otolaryngology and Head and Neck Surgery*, *17*(3), 187–193. http://dx.doi.org/10.1097/MOO.0b013e32832b312a.

Biemesderfer, D., Munger, B. L., Binck, J., & Dubner, R. (1978). The pilo-Ruffini complex: A non-sinus hair and associated slowly-adapting mechanoreceptor in primate facial skin. *Brain Research*, *142*(2), 197–222.

Byers, M. R., & Dong, W. K. (1989). Comparison of trigeminal receptor location and structure in the periodontal ligament of different types of teeth from the rat, cat, and monkey. *Journal of Comparative Neurology*, *279*(1), 117–127. http://dx.doi.org/10.1002/cne.902790110.

Byers, M. R. (1985). Sensory innervation of periodontal ligament of rat molars consists of unencapsulated Ruffini-like mechanoreceptors and free nerve endings. *Journal of Comparative Neurology*, *231*(4), 500–518. http://dx.doi.org/10.1002/cne.902310408.

Cash, R. M., & Linden, R. W. (1982). The distribution of mechanoreceptors in the periodontal ligament of the mandibular canine tooth of the cat. *Journal of Physiology*, *330*, 439–447.

Chambers, M. R., Andres, K. H., von Duering, M., & Iggo, A. (1972). The structure and function of the slowly adapting type II mechanoreceptor in hairy skin. *Quarterly Journal of Experimental Physiology and Cognate Medical Sciences*, *57*(4), 417–445.

Chen, C. C., & Wong, C. W. (2013). Neurosensory mechanotransduction through acid-sensing ion channels. *Journal of Cellular and Molecular Medicine*, *17*(3), 337–349. http://dx.doi.org/10.1111/jcmm.12025.

Cutroneo, G., Piancino, M. G., Ramieri, G., Bracco, P., Vita, G., Isola, G., ... Trimarchi, F. (2012). Expression of muscle-specific integrins in masseter muscle fibers during malocclusion disease. *International Journal of Molecular Medicine*, *30*(2), 235–242. http://dx.doi.org/10.3892/ijmm.2012.986.

Dong, W. K., Shiwaku, T., Kawakami, Y., & Chudler, E. H. (1993). Static and dynamic responses of periodontal ligament mechanoreceptors and intradental mechanoreceptors. *Journal of Neurophysiology*, *69*(5), 1567–1582.

Erzurumlu, R. S., Murakami, Y., & Rijli, F. M. (2010). Mapping the face in the somatosensory brainstem. *Nature Reviews Neuroscience*, *11*(4), 252–263. http://dx.doi.org/10.1038/nrn2804.

Guven, Y., Altunoglu, U., Aktoren, O., Uyguner, Z. O., Kayserili, H., Kaewkahya, M., & Kantaputra, P. N. (2014). Twins with hereditary sensory and autonomic neuropathy type IV with preserved periodontal sensation. *European Journal of Medical Genetics*, *57*(5), 240–246. http://dx.doi.org/10.1016/j.ejmg.2014.02.014.

Habre-Hallage, P., Dricot, L., Hermoye, L., Reychler, H., van Steenberghe, D., Jacobs, R., & Grandin, C. B. (2014). Cortical activation resulting from the stimulation of periodontal mechanoreceptors measured by functional magnetic resonance imaging (fMRI). *Clinical Oral Investigations*, *18*(8), 1949–1961. http://dx.doi.org/10.1007/s00784-013-1174-1.

Hannam, A. G. (1970). Receptor fields of periodontal mechanosensitive units in the dog. *Archives of Oral Biology*, *15*(10), 971–978.
Hayashi, S., Nakakura-Ohshima, K., Ohshima, H., Noda, T., Honma, S., Wakisaka, S., & Maeda, T. (2000). The development of terminal Schwann cells associated with periodontal Ruffini endings in the rat incisor ligament. *Brain Research*, *858*(1), 167–171.
Higuchi, K., Santiwong, P., Tamaki, H., Terashima, T., Nakayama, H., Notani, T., ... Takano, Y. (2008). Development and terminal differentiation of pulp and periodontal nerve elements in subcutaneous transplants of molar tooth germs and incisors of the rat. *European Journal of Oral Sciences*, *116*(4), 324–333. http://dx.doi.org/10.1111/j.1600-0722.2008.00546.x.
Hitomi, Y., Suzuki, A., Kawano, Y., Nozawa-Inoue, K., Inoue, M., & Maeda, T. (2009). Immunohistochemical detection of ENaCbeta in the terminal Schwann cells associated with the periodontal Ruffini endings of the rat incisor. *Biomedical Research*, *30*(2), 113–119.
Honma, S., Taki, K., Lei, S., Niwa, H., & Wakisaka, S. (2010). Immunohistochemical localization of SNARE proteins in dental pulp and periodontal ligament of the rat incisor. *The Anatomical Record (Hoboken)*, *293*(6), 1070–1080. http://dx.doi.org/10.1002/ar.21106.
Honma, S., Kato, A., Shi, L., Yatani, H., & Wakisaka, S. (2012). Vesicular glutamate transporter immunoreactivity in the periodontal ligament of the rat incisor. *The Anatomical Record (Hoboken)*, *295*(1), 160–166. http://dx.doi.org/10.1002/ar.21465.
Hoshino, N., Harada, F., Alkhamrah, B. A., Aita, M., Kawano, Y., Hanada, K., & Maeda, T. (2003). Involvement of brain-derived neurotrophic factor (BDNF) in the development of periodontal Ruffini endings. *The Anatomical Record. Part A, Discoveries in Molecular, Cellular, and Evolutionary Biology*, *274*(1), 807–816. http://dx.doi.org/10.1002/ar.a.10094.
Huang, Y., Corpas, L. S., Martens, W., Jacobs, R., & Lambrichts, I. (2011). Histomorphological study of myelinated nerve fibres in the periodontal ligament of human canine. *Acta Odontologica Scandinavica*, *69*(5), 279–286. http://dx.doi.org/10.3109/00016357.2011.563245.
Igarashi, Y., Aita, M., Suzuki, A., Nandasena, T., Kawano, Y., Nozawa-Inoue, K., & Maeda, T. (2007). Involvement of GDNF and its receptors in the maturation of the periodontal Ruffini endings. *Neuroscience Letters*, *412*(3), 222–226. http://dx.doi.org/10.1016/j.neulet.2006.11.012.
Iggo, A., & Andres, K. H. (1982). Morphology of cutaneous receptors. *Annual Review of Neuroscience*, *5*, 1–31. http://dx.doi.org/10.1146/annurev.ne.05.030182.000245.
Iizuka, N., Suzuki, A., Nozawa-Inoue, K., Kawano, Y., Nandasena, B. G., Okiji, T., & Maeda, T. (2009). Differential cell-specific location of Cav-1 and Ca(2+)-ATPase in terminal Schwann cells and mechanoreceptive Ruffini endings in the periodontal ligament of the rat incisor. *Journal of Anatomy*, *214*(2), 267–274. http://dx.doi.org/10.1111/j.1469-7580.2008.01029.x.
Itoh, S., Nishiura, H., Tabata, T., & Watanabe, M. (2002). Correlations between response properties of periodontal mechanosensitive neurones in the primary somatosensory cortex of the rabbit and cortically induced rhythmical jaw movements. *Archives of Oral Biology*, *47*(6), 481–490.
Jabbar, S., Harada, F., Aita, M., Ohishi, M., Saito, I., Kawano, Y., ... Maeda, T. (2007). Involvement of neurotrophin-4/5 in regeneration of the periodontal Ruffini endings at the early stage. *Journal of Comparative Neurology*, *501*(3), 400–412. http://dx.doi.org/10.1002/cne.21256.
Johnsen, S. E., Svensson, K. G., & Trulsson, M. (2007). Forces applied by anterior and posterior teeth and roles of periodontal afferents during hold-and-split tasks in human subjects. *Experimental Brain Research*, *178*(1), 126–134. http://dx.doi.org/10.1007/s00221-006-0719-9.
Kang, Y. G., Nam, J. H., Kim, K. H., & Lee, K. S. (2010). FAK pathway regulates PGE(2) production in compressed periodontal ligament cells. *Journal of Dental Research*, *89*(12), 1444–1449. http://dx.doi.org/10.1177/0022034510378521.
Kim, S. J., Park, K. H., Park, Y. G., Lee, S. W., & Kang, Y. G. (2013). Compressive stress induced the up-regulation of M-CSF, RANKL, TNF-alpha expression and the down-regulation of OPG expression in PDL cells via the integrin-FAK pathway. *Archives of Oral Biology*, *58*(6), 707–716. http://dx.doi.org/10.1016/j.archoralbio.2012.11.003.
Klineberg, I. J., Trulsson, M., & Murray, G. M. (2012). Occlusion on implants—Is there a problem? *Journal of Oral Rehabilitation*, *39*(7), 522–537. http://dx.doi.org/10.1111/j.1365-2842.2012.02305.x.
Korkmaz, Y., Bloch, W., Klinz, F. J., Kubler, A. C., Schneider, K., Zimmer, S., ... Raab, W. H. (2009). The constitutive activation of extracellular signal-regulated kinase 1 and 2 in periodontal ligament nerve fibers. *Journal of Periodontology*, *80*(5), 850–859. http://dx.doi.org/10.1902/jop.2009.080550.
Leyhausen, P. (1982). *Katzen, eine verhaltenskunde*, 6. aufl. ed. Berlin Hamburg: Parey.
Linden, R. W., & Scott, B. J. (1989). Distribution of mesencephalic nucleus and trigeminal ganglion mechanoreceptors in the periodontal ligament of the cat. *Journal of Physiology*, *410*, 35–44.
Lobbezoo, F., Trulsson, M., Jacobs, R., Svensson, P., Cadden, S. W., & van Steenberghe, D. (2002). Topical review: Modulation of trigeminal sensory input in humans: Mechanisms and clinical implications. *Journal of Orofacial Pain*, *16*(1), 9–21.
Lund, J. P., & Kolta, A. (2006). Generation of the central masticatory pattern and its modification by sensory feedback. *Dysphagia*, *21*(3), 167–174. http://dx.doi.org/10.1007/s00455-006-9027-6.
Ma, T., Gao, H., Fang, X., & Yang, H. (2012). Water channel proteins in the peripheral nervous system in health and disease. *Molecular Aspects of Medicine*, *33*(5–6), 605–611. http://dx.doi.org/10.1016/j.mam.2012.03.002.
Maeda, T., Ochi, K., Nakakura-Ohshima, K., Youn, S. H., & Wakisaka, S. (1999). The Ruffini ending as the primary mechanoreceptor in the periodontal ligament: Its morphology, cytochemical features, regeneration, and development. *Critical Reviews in Oral Biology and Medicine*, *10*(3), 307–327.
Maruyama, Y., Harada, F., Jabbar, S., Saito, I., Aita, M., Kawano, Y., ... Maeda, T. (2005). Neurotrophin-4/5-depletion induces a delay in maturation of the periodontal Ruffini endings in mice. *Archives of Histology and Cytology*, *68*(4), 267–288.
Miki, K., Honma, S., Ebara, S., Kumamoto, K., Murakami, S., & Wakisaka, S. (2015). Changes in the distribution of periodontal nerve fibers during dentition transition in the cat. *Public Library of Science*, *10*(6), e0129826. http://dx.doi.org/10.1371/journal.pone.0129826.
Mishra, S. K., Chowdhary, R., Chrcanovic, B. R., & Branemark, P. I. (2016). Osseoperception in dental implants: A systematic review. *Journal of Prosthodontics*, *25*(3), 185–195. http://dx.doi.org/10.1111/jopr.12310.
Morquette, P., Lavoie, R., Fhima, M. D., Lamoureux, X., Verdier, D., & Kolta, A. (2012). Generation of the masticatory central pattern and its modulation by sensory feedback. *Progress in Neurobiology*, *96*(3), 340–355. http://dx.doi.org/10.1016/j.pneurobio.2012.01.011.
Nagata, K., Itoh, S., Tsuboi, A., Takafuji, Y., Tabata, T., & Watanabe, M. (2008). Response properties of periodontal mechanosensitive neurons in the trigeminal ganglion of rabbit and neuronal activities during grinding-like jaw movement induced by cortical stimulation. *Archives of Oral Biology*, *53*(12), 1138–1148. http://dx.doi.org/10.1016/j.archoralbio.2008.06.007.
Nakakura-Ohshima, K., Maeda, T., Ohshima, H., Noda, T., & Takano, Y. (1995). Postnatal development of periodontal ruffini endings in rat incisors: An immunoelectron microscopic study using protein gene product 9.5 (PGP 9.5) antibody. *Journal of Comparative Neurology*, *362*(4), 551–564. http://dx.doi.org/10.1002/cne.903620409.
Nishiura, H., Tabata, T., & Watanabe, M. (2000). Response properties of slowly and rapidly adapting periodontal mechanosensitive neurones in the primary somatosensory cortex of the cat. *Archives of Oral Biology*, *45*(10), 833–842.
Ochi, K., Wakisaka, S., Youn, S. H., Hanada, K., & Maeda, T. (1997). Calretinin-like immunoreactivity in the Ruffini endings, slowly adapting mechanoreceptors, of the periodontal ligament of the rat incisor. *Brain Research*, *769*(1), 183–187.
Ohishi, M., Harada, F., Rahman, F., Saito, I., Kawano, Y., Nozawa-Inoue, K., & Maeda, T. (2009). GDNF expression in terminal schwann cells associated with the periodontal ruffini endings of the rat incisors during nerve regeneration. *The Anatomical Record (Hoboken)*, *292*(8), 1185–1191. http://dx.doi.org/10.1002/ar.20931.
Piancino, M. G., & Kyrkanides, S. (2016). *Understanding masticatory function in unilateral crossbites*. Ames, Iowa: John Wiley & Sons Inc..
Piancino, M. G., Talpone, F., Dalmasso, P., Debernardi, C., Lewin, A., & Bracco, P. (2006). Reverse-sequencing chewing patterns before and after treatment of children with a unilateral posterior crossbite. *European Journal of Orthodontics*, *28*(5), 480–484. http://dx.doi.org/10.1093/ejo/cjl014.
Piancino, M. G., Bracco, P., Vallelonga, T., Merlo, A., & Farina, D. (2008). Effect of bolus hardness on the chewing pattern and activation of masticatory muscles in subjects with normal dental occlusion. *Journal of Electromyography and Kinesiology*, *18*(6), 931–937. http://dx.doi.org/10.1016/j.jelekin.2007.05.006.
Piancino, M. G., Farina, D., Talpone, F., Merlo, A., & Bracco, P. (2009). Muscular activation during reverse and non-reverse chewing cycles in unilateral posterior crossbite. *European Journal of Oral Sciences*, *117*(2), 122–128. http://dx.doi.org/10.1111/j.1600-0722.2008.00601.x.
Piancino, M. G., Isola, G., Merlo, A., Dalessandri, D., Debernardi, C., & Bracco, P. (2012). Chewing pattern and muscular activation in open bite patients. *Journal of Electromyography and Kinesiology*, *22*(2), 273–279. http://dx.doi.org/10.1016/j.jelekin.2011.12.003.
Piancino, M. G., Falla, D., Merlo, A., et al. (2016). Effects of therapy on masseter activity and chewing kinematics in patients with unilateral posterior crossbite. *Archives of Oral Biology*, *67*(July), 61–67.
Rahman, F., Harada, F., Saito, I., Suzuki, A., Kawano, Y., Izumi, K., ... Maeda, T. (2011). Detection of acid-sensing ion channel 3 (ASIC3) in periodontal Ruffini endings of mouse incisors. *Neuroscience Letters*, *488*(2), 173–177. http://dx.doi.org/10.1016/j.neulet.2010.11.023.
Ramieri, G. A., Schierano, G., Spada, M. C., Giovando, M. L., Verze, L., & Preti, G. (2004). Growth-associated protein-43 immunoreactivity in human oral mucosa in dentate subjects, in edentulous patients and after implant-anchored rehabilitation. *Clinical Oral Implants Research*, *15*(1), 66–72.
Ratajczak, J., Bronckaers, A., Dillen, Y., Gervois, P., Vangansewinkel, T., Driesen, R. B., ... Hilkens, P. (2016). The neurovascular properties of dental stem cells and their importance in dental tissue engineering. *Stem Cells International*, *976287*, . http://dx.doi.org/10.1155/2016/9762871.
Ratajczak, J., Hilkens, P., Gervois, P., Wolfs, E., Jacobs, R., Lambrichts, I., & Bronckaers, A. (2016). Angiogenic capacity of periodontal ligament stem cells pretreated with deferoxamine and/or fibroblast growth factor-2. *Public Library of Science*, *11*(12), e0167807. http://dx.doi.org/10.1371/journal.pone.0167807.
Saito, S., Suzuki, A., Nozawa-Inoue, K., Kawano, Y., Hoshino, M., Saito, C., & Maeda, T. (2009). Immunohistochemical detection of nestin in the periodontal Ruffini endings of the rat incisor. *Neuroscience Letters*, *449*(3), 195–200. http://dx.doi.org/10.1016/j.neulet.2008.11.001.
Shi, L., Atsumi, Y., Kodama, Y., Honma, S., & Wakisaka, S. (2006). Requirement of proper occlusal force for morphological maturation of neural components of periodontal Ruffini endings of the rat incisor. *Archives of Oral Biology*, *51*(8), 681–688. http://dx.doi.org/10.1016/j.archoralbio.2006.02.006.
Sodeyama, T., Maeda, T., Takano, Y., & Hara, K. (1996). Responses of periodontal nerve terminals to experimentally induced occlusal trauma in rat molars: An

immunohistochemical study using PGP 9.5 antibody. *Journal of Periodontal Research*, *31*(4), 235–248.
Sowman, P. F., Ogston, K. M., & Turker, K. S. (2007). Periodontal anaesthetisation decreases rhythmic synchrony between masseteric motor units at the frequency of jaw tremor. *Experimental Brain Research*, *179*(4), 673–682. http://dx.doi.org/10.1007/s00221-006-0824-9.
Svensson, K. G., & Trulsson, M. (2011). Impaired force control during food holding and biting in subjects with tooth- or implant-supported fixed prostheses. *Journal of Clinical Periodontology*, *38*(12), 1137–1146. http://dx.doi.org/10.1111/j.1600-051X.2011.01781.x.
Tabata, T., & Hayashi, H. (1994). Physiological properties of periodontal mechanosensitive neurones in the trigeminal (Gasserian) ganglion of the rat. *Archives of Oral Biology*, *39*(5), 379–385.
Tabata, T., Yamaki, A., Takahashi, Y., & Hayashi, H. (2002). Physiological properties of periodontal mechanosensitive neurones in the posteromedial ventral nucleus of rat thalamus. *Archives of Oral Biology*, *47*(9), 689–694.
Tabata, T., Takahashi, Y., & Hayashi, H. (2006). Physiological properties of molar-mechanosensitive periodontal neurons in the trigeminal ganglion of the rat. *Archives of Oral Biology*, *51*(9), 729–735. http://dx.doi.org/10.1016/j.archoralbio.2006.03.003.
Trulsson, M., & Essick, G. K. (2010). Sensations evoked by microstimulation of single mechanoreceptive afferents innervating the human face and mouth. *Journal of Neurophysiology*, *103*(4), 1741–1747. http://dx.doi.org/10.1152/jn.01146.2009.
Trulsson, M. (2007). Force encoding by human periodontal mechanoreceptors during mastication. *Archives of Oral Biology*, *52*(4), 357–360. http://dx.doi.org/10.1016/j.archoralbio.2006.09.011.
Tsutsumi, T., Kajiya, H., Fukawa, T., Sasaki, M., Nemoto, T., Tsuzuki, T., . . . Okabe, K. (2013). The potential role of transient receptor potential type A1 as a mechanoreceptor in human periodontal ligament cells. *European Journal of Oral Sciences*, *121*(6), 538–544. http://dx.doi.org/10.1111/eos.12083.
Umemura, T., Yasuda, K., Ishihama, K., Yamada, H., Okayama, M., Hasumi-Nakayama, Y., & Furusawa, K. (2010). A comparison of the postnatal development of muscle-spindle and periodontal-ligament neurons in the mesencephalic trigeminal nucleus of the rat. *Neuroscience Letters*, *473*(2), 155–157. http://dx.doi.org/10.1016/j.neulet.2010.02.043.
Wakisaka, S., Atsumi, Y., Youn, S. H., & Maeda, T. (2000). Morphological and cytochemical characteristics of periodontal Ruffini ending under normal and regeneration processes. *Archives of Histology and Cytology*, *63*(2), 91–113.
Ziegler, N., Alonso, A., Steinberg, T., Woodnutt, D., Kohl, A., Mussig, E., . . . Tomakidi, P. (2010). Mechano-transduction in periodontal ligament cells identifies activated states of MAP-kinases p42/44 and p38-stress kinase as a mechanism for MMP-13 expression. *BMC Cell Biology*, *11*, 10. http://dx.doi.org/10.1186/1471-2121-11-10.