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ORIGINAL ARTICLE

Histomorphological study of myelinated nerve fibres in the periodontal ligament of human canine

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Abstract

Objective. This study aims to describe the human periodontal ligament (PDL) using serial sections, with a focus on mechanoreceptor distribution and morphology. ***Materials and methods.*** One permanent lower canine with surrounding PDL and alveolar bone tissues was retrieved from a human cadaver. After being embedded into paraffin block, the canine was horizontally cut in 6 μm thick serial sections. At root levels of 0.3, 1.5, 3, 4.5 and 6 mm from the apex, five slices each level were evaluated. Immunocytochemisty was performed on the same serial sections, enabling a more reliable description of neural structures. ***Results.*** The distribution of myelinated fibres varied from apical to coronal level, with a total number of 38 at 0.3 mm from the apex, 25 at 1.5 mm, 25 at 3 mm, 31 at 4.5 mm and 32 at 6 mm. At all times, mesial and buccal regions were typically more densely innervated ($p < 0.01$) except at the 3 mm level. The average density of myelinated nerve fibres increased by arriving closer to the apex. However, the average diameter did not show any significant differences amongst quadrants or root levels ($p > 0.05$). The average diameter of myelinated fibres varied between 5.3–7.8 μm. Grouped myelinated axons were twice as common as isolated ones, with the innervation being rather close to the alveolar bone. Isolated myelinated axons showed a tendency to group around large blood vessels. ***Conclusion.*** The present results add to the understanding of human PDL innervation, indicating dense innervations by myelinated nerve fibres in close proximity to collagen fibres and alveolar bone. It also reveals that apical as well as mesial and buccal sites of the human canine are more densely innervated.

Key Words: *Canine, histology, myelinated nerve fibre, periodontal ligament, tactile function*

Introduction

The periodontal ligament (PDL) is part of the complex supporting structures around the tooth being highly involved in oral physiological actions, such as tooth support, protection, load distribution to bone and sensory feedback. All these actions are not separated from the primary role of mechanosensitive afferent nerve fibres. By the afferent nerve in the PDL, forces can be transmitted to the surrounding bone and lead to afferent nerve signals [1]. This periodontal neural feedback is strongly related to the existence of myelinated structures in the PDL [2–4]. The rich innervation indeed guarantees a rapid and efficient conduction of action potentials along axons [5].

It is currently believed that mechanoreceptive terminals in the PDL are predominantly derived from myelinated nerve fibres owing to specialized terminals, such as Ruffini endings [6–8]. A previous study on the innervation of 10 adult cat canines found that apical fibres were generally larger than the coronal ones [9]. It was demonstrated that the lingual PDL in hamster incisors was exclusively innervated by Ruffini endings by means of electron microscopy [10]. Neurofilament protein immunoreactive nerve fibres were also found to be densely distributed in the apical third of the PDL of dog incisors and canines [11]. It should be stressed that existing evidence is usually based on animal studies. Only a few studies concentrated on the PDL of human teeth and, if doing so, these were

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mainly focusing on the ultrastructure of the epithelial rests of Malassez (ERM) or nerve endings [12–14]. It is evident that those human studies are more valuable, yet on the other hand these are unable to show the true immunohistochemical identification. Recently, Becktor et al. [15] further described the distribution of ERM cells in the human PDL by an immunohistochemical technique, while the spatial interrelation of peripheral nerves and ERM in the human PDL were examined by Kjaer and Nolting [16]. To date, the knowledge on the precise location and content of the myelinated nerve fibres in the human PDL of a tooth using light microscopy is far from complete.

The purpose of the present study was to unravel myelinated axon content and report on the neural distribution and morphology in the PDL of human canine sample. With the immunocytochemical technique and light microscopy to identify and quantify myelinated nerve fibres, the present study could offer a more quantitative evaluation on the distribution than those using electron microscopy.

Materials and methods

The following experiment was carried out according to the local ethical guidelines, on a patient who had donated his body to the Department of Anatomy (University of Hasselt).

Light microscopy observation

One periodontally healthy permanent mandibular canine with its surrounding PDL and alveolar bone tissues was retrieved from a human cadaver (male Caucasian, 73 years old). The time interval between the death of the donor and the start of histological fixation was 5 days. The specimens were fixed in 10% formalin solution for 3 days and decalcified in 5% nitric acid, followed by dehydration through a graded concentration of ethanol and embedding in paraffin. In total, 2003 thin serial sections with a thickness of 6 μm were horizontally sectioned using a Reichert microtome (Reichert, Wien, Austria), then mounted, cleared in xylol, stained with the Masson trichrome stain and finally digitized by a high resolution Mirax Scan (Carl Zeiss Micro imaging GmbH, Germany). Observations were performed by one experienced observer at a magnification of 50× with a 30 inch LCD monitor (Apple Inc., Cupertino, CA, USA) at five root levels (0.3, 1.5, 3, 4.5 and 6 mm from the apex, respectively). Within all the digitized sections scanned for observations, five sections at each root level were randomly selected and averaged to quantify the number and density (number/area) of myelinated nerve fibres at five levels in the PDL of the canine.

To establish any regional changes in the number and diameter of myelinated nerve fibres, at each root level, the PDL was divided into four quadrants—buccal, distal, lingual and mesial, with a sector of 90° allocated to each region (Figure 1A). The area of each region and the lesser diameter of myelinated nerve fibres (including the axon and its respective myelin sheaths observed under the light microscopy) in each region were manually selected and measured with a dedicated image software package (Mirax Viewer 1.1, Göttingen, Germany). To prevent the distortion which occurs when a nerve fibre is cut obliquely during the biopsy, the lesser diameter is considered as a better parameter which can represent the diameter of a non-circular fibre [17]. The fibres partially at the borderline of two regions were excluded.

The myelinated axons were classified into two groups (Figures 1B and C): 'grouped' axons, which were those situated predominantly in the alveolar related part of the PDL (adjacent to the bone) and 'isolated' axons, which existed as individuals and were

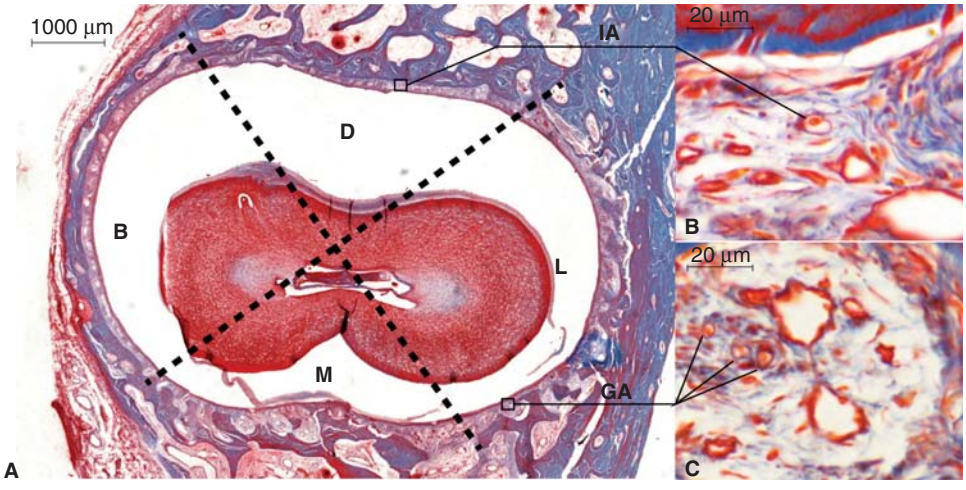

Figure 1. Horizontal section of the canine root with the projected line used for histomorphometrical evaluation of four quadrants of the periodontal ligament (B = buccal; D = distal; L = lingual; M = mesial; IA = isolated myelinated axons; GA = grouped myelinated axons).

situated mainly in the area of the root cementum. In this study, 'isolated' axon was defined as an axon around which there was no more than one axon in a 20 μm range.

Immunocytochemistry

Immunocytochemical stainings were performed on four sections randomly selected from the same serial sections at a root level of 2 mm from the apex, using the peroxidase-based EnVision System (DakoCytomation, Glostrup, Denmark). The sections were deparaffinized and washed for 30 min at 4°C in 0.01 M phosphate buffered saline (PBS). Non-specific binding sites were blocked with 3% normal goat serum in PBS. After washing in PBS, the sections were incubated with the primary mouse monoclonal antibody against the neurofilament protein (Abcam, Cambridge, UK) for 1 h, washed again and incubated for 30 min with goat anti-mouse horseradish peroxidase-conjugated secondary antibodies. A highly sensitive diaminobenzidine chromogenic substrate system was used to visualize the peroxidase. After mounting in an aqueous mounting medium (Aquatex, Merck, Darmstadt, Germany), the tissue was examined using a photomicroscope equipped with an automated camera (Nikon Eclipse 80i, Nikon Co., Japan). Control tissues were subjected to the same immunoperoxidase staining, with omission of the primary antibody.

Statistical analysis

A statistical software R package (version 2.8.1) was used for statistical analysis. Data were analysed by descriptive statistics and presented as mean (SD). The two-way ANOVA test ($\alpha = 0.05$) followed by post-hoc Tukey's procedure allowed multiple comparisons between the five root levels and four quadrants. Pearson's correlation was used to compare the average density and average diameter of myelinated nerve fibres at five root levels.

Results

The PDL tissue examined around the canine sample was healthy and normal. The tooth, from the tip of the crown to the root apex, measured 22 mm in length, and the tooth root, from the apex to the alveolar crest, measured ~ 13 mm.

In the investigated canine sample, coarse nerve fibre bundles were mostly found in the vicinity of blood vessels and branched frequently (Figure 2). Neurovascular structures appeared to enter in the alveolar bone or vice versa, creating an inter-digitating relationship between PDL structures and alveolar bone.

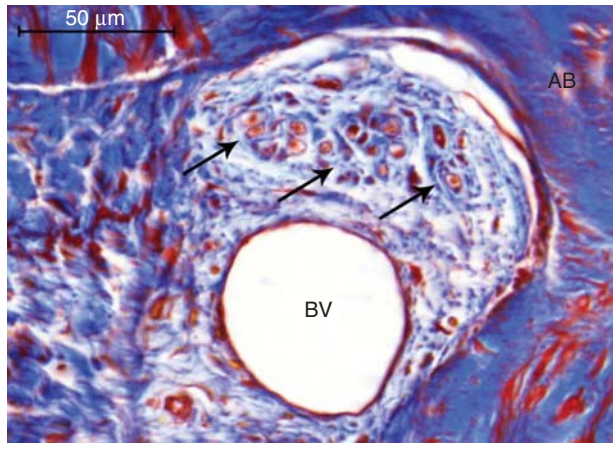

Figure 2. Richly innervated area in the periodontal ligament (PDL): grouped and isolated myelinated nerve fibres related or not with a blood vessel were present in the PDL, mainly in the apical region. Arrows identify grouped myelinated axons in the vicinity of blood vessels (BV = blood vessel; AB = alveolar bone).

Neurofilament immunoreactivity was demonstrated by the immunocytochemisty (Figure 3). The myelinated nerve fibres around a blood vessel were clearly visualized in the sections stained for neurofilament protein. The number of isolated myelinated axons was only half as many as that of grouped ones (Table I). The grouped myelinated axons were frequently observed at the alveolar-related part of the PDL, with a proportion of 83%, while the rest were present in the vicinity of the cementum. The isolated axons at the alveolar-related part held 61%, though the number of isolated myelinated axons was still less than that of the grouped ones.

As shown in Table II, the average diameter of myelinated axons in the PDL of this canine varied between 5.3–7.8 μm when myelinated. The average

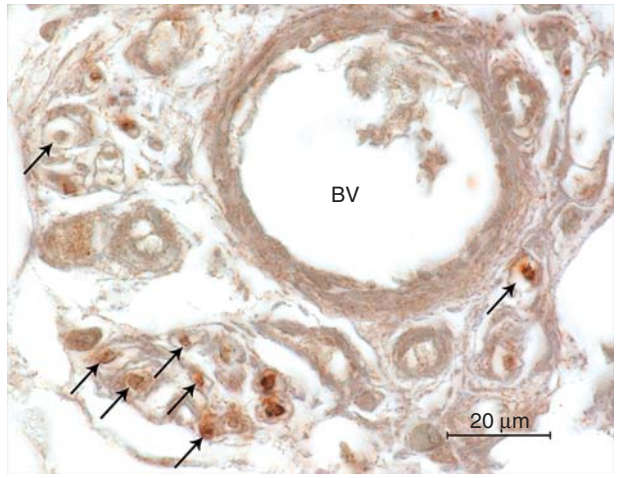

Figure 3. Immunocytochemical image of myelinated nerve fibres (as indicated by arrows) labelled with an antibody against the neurofilament protein. The brown colour is caused by the diaminobenzidine staining via the secondary antibody (BV = blood vessel).

Table I. Average number of grouped and isolated myelinated axons in the periodontal ligament (PDL) of the human canine sample at five root levels.

	0.3 mm		1.5 mm		3 mm		4.5 mm		6 mm		Total	
Groups	ARP	CRP	ARP	CRP	ARP	CRP	ARP	CRP	ARP	CRP	ARP	CRP
GA	25	6	14	3	10	1	21	4	19	4	89	18
IA	5	2	5	3	8	6	3	3	6	3	27	17
Total	30	8	19	6	18	7	24	7	25	7	116	35

ARP = alveolar-related part of PDL; CRP = cementum-related part of PDL; GA = grouped axons; IA = isolated axons.

diameter did not show any significant difference in four quadrants or at five root levels ($p > 0.05$).

The average number of myelinated axons in the PDL at level of 0.3 mm from the apex was 38, sharing ~ 25.2% of five root levels, followed by 6 mm from the apex with 21.2%, 4.5 mm from the apex 20.5%, 3 mm and 1.5 mm with the same 21.8% (Figure 4).

The average density of myelinated axons was highest at a level of 0.3 mm from the apex, while the lowest value occurred at a distance of 6 mm from the apex (Figure 5). Furthermore, there were buccal peaks and mesial peaks of density distribution at all levels ($p < 0.01$) except at the 3 mm level.

Pearson's correlation indicated that there was no linear correlation between average diameter and average density ($r^2 = 0.12$).

Three histological sections presented a relationship between myelinated axons and blood vessels in the buccal PDL at the coronal level (level of 10 mm from the apex) (Figure 6). The isolated myelinated axon showed a tendency to move towards grouped axons around large blood vessels from the bottom upwards.

Discussion

PDL innervation plays a primary role in oral tactile function, allowing one to feel a 1-gram loading or to detect interocclusal strips of 20 μm [2]. This extremely sensitive system may thus allow one to modulate motoric function. Indeed it may allow one to modulate or even refine the central masticatory pattern [18]. While muscular activity increases when chewing harder food, it drops when nerves supplying the periodontal receptors are cut. This suggests that the periodontal afferents are responsible for some adaptation or modulation to the food hardness.

Literature on a description of PDL innervation mainly covers papers on small animal PDL [6,7,9–11,19–22]. Three types of nerve endings were identified under electron microscopy, including free nerve endings (originating from myelinated and unmyelinated nerve fibres), Ruffini-like endings (mostly found at the apical part of the PDL) and lamellated corpuscles [12,14,23]. Lambrichts et al. [12] and Fukuda and Tazaki [14] are the few authors who focused on human PDL. It is important, however, to stress that only the tooth-related parts of human PDL were observed. This could be confirmed in the present study by serial sections on a complete human PDL.

The nerve structures observed in the present study were myelinated nerve fibres, which was further confirmed by immunocytochemistry. The average diameter of nerve fibres in our study was within the range of that found by Lambrichts et al. [12] under electron microscopy, which was 1–14 μm based on the data from anterior and posterior teeth. The results may indicate a variation of diameter of nerve fibres in human PDL between different tooth sites. While two previous studies on the innervation of cat canines noted that apical fibres were generally larger than the coronal ones [9,19], the present study did not find a significant difference on the diameter between the evaluated levels. Whether this discrepancy reflects

Table II. Average diameter of myelinated axons in the periodontal ligament of the human canine sample (μm).

	0.3 mm		1.5 mm		3 mm		4.5 mm		6 mm	
Quadrants	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mesial	6.1	2.0	7.0	2.2	7.5	2.4	7.3	2.4	6.9	2.5
Lingual	5.9	2.1	5.3	1.7	8.0	1.8	6.1	1.8	7.4	3.5
Distal	6.6	1.9	5.6	1.5	7.8	2.1	6.8	1.7	5.9	1.8
Buccal	6.3	2.0	5.9	2.2	7.1	2.1	6.3	2.3	6.4	2.5

No statistical differences were found in four quadrants per level ($\alpha = 0.05$).

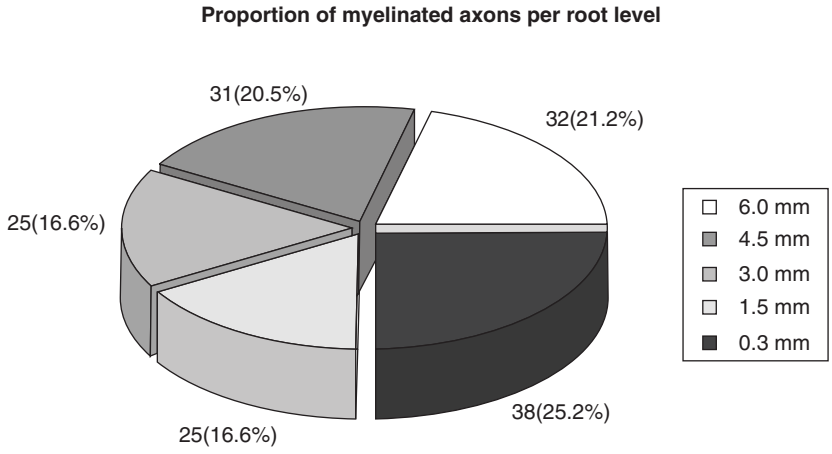

Figure 4. Pie chart of average number of myelinated axons in the periodontal ligament of the human canine sample at five root levels.

differences on the diameter distribution in the PDL of cats and humans or not remains to be determined on larger samples and controlled studies. To find any potential links between morphological characters and physiological functions of mechanoreceptors, it seems essential to further acquire information from human periodontal specimens rather than from animal ones.

The present study reaches much the same conclusion as the previous study [12] on human teeth, which declared 31% of Ruffini-like receptors in the apical part of the tooth-related ligament. Another two studies on the canines of dogs and cats reported similar results by revealing the dense distribution of nerve fibres at the apical third of tooth [11,21]. It provides other evidence that the Ruffini endings are derived from myelinated axons. Although the densities of axons at level of 1.5, 3, 4.5 and 6 mm were not high, axons demonstrated a wider morphology, quantificationally represented by their larger diameters. Pearson's correlation failed to show, however, a negative linear relationship between the average diameter and the average density. The relationship between the diameter and distribution of myelinated axons needs further investigation.

Loescher and Holland [19] divided the myelinated axons into two groups: grouped and isolated axons. In order to improve analytic precision, isolated axons were further defined as 'there was no more than one axon in a 20 μm range' in the present study. Another interesting observation was that the isolated

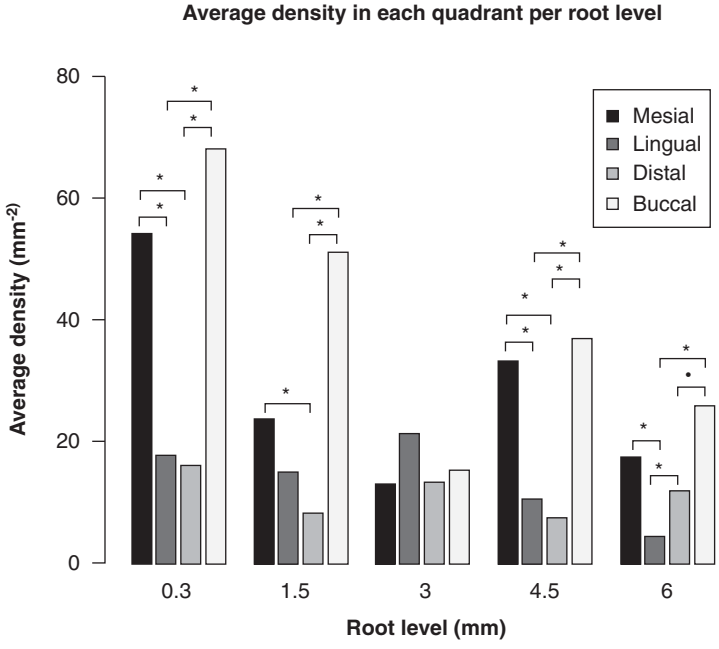

Figure 5. Average density of myelinated axons in different quadrants per level. Asterisks indicate the statistical difference ($\alpha < 0.05$) of density within each level. At 0.3 and 4.5 mm level, both the buccal and mesial density were significantly higher than the lingual and distal density; at 1.5 mm level, the buccal density was significantly higher than the lingual and distal density, while the mesial density was only significantly higher than the distal density; at 3 mm level, no significant differences in density were found within four quadrants; at 6 mm level, both the buccal and mesial density showed significant differences compared with the lingual density (Significant codes: $*P < 0.01$, • $0.05 < P > 0.1$).

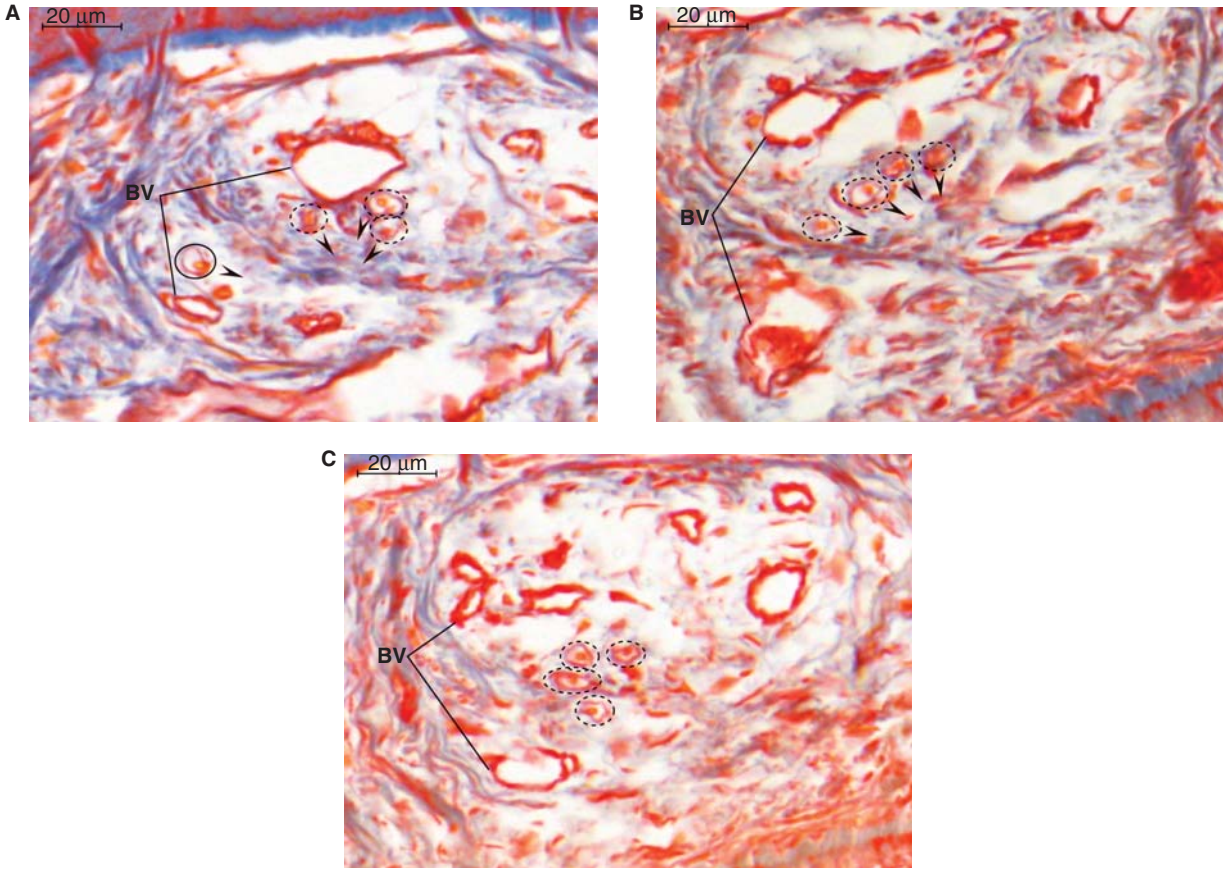

Figure 6. One bundle of grouped myelinated nerve fibres distributed in the mesial quadrant at coronal level of the canine root. Dotted circles indicate examples of grouped myelinated axons and solid circles indicate examples of isolated myelinated axons (BV = blood vessel; from A–C = from bottom upwards). (A) A group of three myelinated fibres were accompanied by a larger blood vessel, while an isolated myelinated axon was accompanied by a smaller blood vessel. (B) When the smaller blood vessel concoursed with a distant blood vessel, the isolated myelinated axon gradually joined the previous grouped ones. (C) Finally the isolated myelinated axon became a large bundle of one grouped myelinated axons, achieving a new innervation.

myelinated axon at coronal level had a tendency to move towards grouped axons around large diameter blood vessels when viewed from the bottom up. It is expected, however, that the trends between these two kinds of axons allow a more refined analysis at all root levels. Both grouped and isolated myelinated axons were frequently observed in the alveolar related part of the PDL. This is probably due to the fact that the location has more nutrient supply coming from alveolar bone. The function of these myelinated axons may be directly or indirectly related to the remodelling of periodontal tissues.

The free nerve endings and lanceolated terminals are regarded as nociceptors for pain and heat, although a mechanoreceptor function cannot be excluded [12]. Byers and Maeda [23] reported that the Ruffini receptors were thought to be stretch mechanoreceptors of the slowly-adapting type, which are now considered as the saturating receptors [24]. The Ruffini-like receptors might have a similar function. The lamellated endings might be mechanoreceptors of rapidly-adapting type and later considered as non-saturating receptors [24]. Among many morphologically different periodontal mechanoreceptors, the Ruffini ending receptor is the primary mechanoreceptor in the human [14] and other mammalian ligament [25,26]. These findings are probably related with the dense innervation by myelinated axons observed in the present study. Given the distribution of the myelinated axons in the PDL it can be supposed that the corresponding mechanoreptor functions in different root levels are not uniform. Imai et al. [25] further pointed out parts of periodontal Ruffini endings can regenerate following nerve cross-anastomosis with mental nerve. Regeneration of nerve fibres around the extracted teeth and dental implants is still under investigation. A recent paper described the reinnervation of the ERM following autotransplantation of third molars [27].

It has been previously described that the majority of Ruffini-like receptors lacked any form of capsule [6,12,22]. The direct contact between the receptors and the oriented collagen fibres can be linked to the transducing process of mechanical stimuli in PDL. By means of immunohistochemistry for nervous-specific

proteins and electron microscopy, Maeda et al. [22] and Kannari [10] found that the lingual PDL in rodent incisors, such as in rats and hamsters, was exclusively innervated by Ruffini endings, whereas the labial PDL was lacking this type of nerve terminals. Similarly, the present study showed myelinated axons in the human PDL were mainly distributed in the alveolar-related part. It demonstrated, however, that myelinated axons were more frequently innervated in the buccal and mesial regions rather than lingual regions of the human PDL. Although it is hard to say whether these axons respond to tension or compression in the location where they are situated, there is a potential link between the location, types and physiological function of mechanoreceptors in human PDL.

It should be pointed out that this study has examined myelinated nerve fibres only on a lower canine sample. The distribution of the nerve fibres in the PDL of human teeth is probably dependent on different tooth sites and types of occlusion. Study on the distribution of receptors by neuro-recording in the human PDL from anterior teeth to molars indicated a decreasing number of receptors distally along the dental arch [28], which attests to the importance of a well-developed mechanoreceptive innervation of the anterior part of the mouth. Not only the distribution of myelinated axons on human canines but also that on posterior teeth in a larger sample may be of future interest.

Notwithstanding its limitations, the present study is the first serial section approaching at the light microscopy level performed in humans. It proves that the innervation of PDL is changing according to different root levels. The largest density of myelinated structure appeared at the apical level, while the smallest value occurred at the middle level of root. The number of grouped myelinated axons were twice as common as that of isolated ones. Both of them were mainly located in the alveolar-related part of the PDL.

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