Effect of Inferior Alveolar Nerve Transection on the Inorganic Component of Molars of Rat Mandible

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Abstract: The objective of the study was to determine the effects of inferior alveolar nerve transection on inorganic components in mandibular molars of the rat. We used 26 male laboratory rats of the Wistar strain for the study, age 7–9 weeks. The rats were divided in three groups. The control group (intact) included 6 rats. The surgery was performed under general anesthesia. The experimental group included (group with the nerve transected on the left) included 12 rats. The sham group (group with the nerve prepared without transection) included 8 rats. The animals were sacrificed after 4 weeks. Molars from the left and right sides of the mandible were extracted. Element content levels were determined using inductively coupled plasma mass spectrometry. The following elements were determined in all samples: magnesium (Mg), sodium (Na), potassium (K), calcium (Ca), zinc (Zn), and strontium (Sr). The nerve transection caused: a reduction of the contents of Ca and Sr in the mandibular molars; an increase in the contents of Mg and Zn; a difference arrangement of both sides for Na. The surgery approach itself caused a decrease in the contents of Na and K in the experimental and sham groups; the difference in K in M3 between the left and right sides disappeared due to the surgery. Our results have confirmed the hypothesis of inferior alveolar nerve transection having an effect on inorganic components in mandibular molars in the rat.

Introduction

The pulp is innervated by sensory nerve fibers, forming the subodontoblastic plexus and continuing into the odontoblast layer and dentinal tubules (Berkovitz, 2016) as free nerve endings (Fristad, 1997). The nerve supply of the dentin-pulp complex is mainly made up of A fibers (both delta and beta) and C fibers. They are classified according to their diameter and their conduction velocity. The A fibers are mainly stimulated by an application of cold, producing sharp pain, whereas stimulation of the C fibers produces a dull aching pain. Because of their location and arrangement, the C fibers are responsible for referred pain (Abd-Elmeguid and Yu, 2009). Furthermore, the pulp is innervated by vasoconstrictor sympathetic nerve fibres (Berkovitz, 2016).

Nerve endings contained in the pulp release various neuropeptides with an impact on the homeostasis (Fristad, 1997; Byers et al., 2003; Berkovitz, 2016). As reported by Jacobsen and Heyeraas (1996), neuropeptides such as CGRP (calcitonin gene-related peptide) and substance P are involved in dentin production. The authors have published information on the effects of capsaicin and of a transection of the inferior alveolar nerve (IAN) on first molar dentin production in the rat. As follows from the study, capsaicin reduced CGRP- and substance P-immunoreactive fibrils in the pulp. A transection of the IAN resulted in an almost complete loss of immunoreactive fibrils in the pulp. Dentin production was reduced in both groups compared to the control (Jacobsen and Heyeraas, 1996).

IAN injury can occur in the fracture of the mandible (Singh et al., 2016), in various surgical procedures in the mandible or in the course of endodontic treatment

(Baxmann, 2006; Ozkan et al., 2008). IAN lesion can be caused by a pathological process (Ozkan et al., 2008). This nerve damage may be either temporary or permanent (Bhat and Cariappa, 2012).

The teeth (enamel, dentin and cementum) contain organic and inorganic components (Abou Neel et al., 2016). Calcium is one of essential elements in the teeth. Calcium is found there in the form of hydroxyapatite, which also includes phosphorus (Dermience et al., 2015). Calcium metabolism disorders are reflected in changes of tooth structure and properties (Wilhelm, 2007). Various studies have focused on analyzing chemical elements present in the teeth (Curzon and Crocker, 1978; Curzon and Cutress, 1983; Vrbič et al., 1987; Lane and Peach, 1997; Reitznerová et al., 2000; Fischer et al., 2009, 2013; Ghadimi et al., 2013). Curzon and Crocker (1978) studied trace elements with respect to caries; as found by these authors, fluorine, aluminium, iron, selenium and strontium are associated with a low risk of developing caries, while manganese, copper and cadmium are associated with a high risk.

Minimum information on the effects of sensory innervation on inorganic components of tooth structure is found in the literature (Němec et al., 2018a).

In our previous study, we have determined 14 elements in the bone and teeth of the mandible of rat (magnesium, sodium, potassium, calcium, manganese, iron, cobalt, nickel, copper, zinc, rubidium, strontium, molybdenum and barium) (Němec et al., 2018b).

For the purposes of this study, we analysed the following elements: magnesium (Mg), sodium (Na), potassium (K), calcium (Ca), zinc (Zn), and strontium (Sr).

A change of inorganic components of tooth structure due to an innervation disorder can be manifested by altered properties of the given tissue. The objective of the study was to determine the effects of IAN transection on inorganic components in mandibular molars of the rat.

Material and Methods

Experimental animals

We used 26 male laboratory rats of the Wistar strain, age 7–9 weeks and weight 320–405 g. The animals were obtained from the breeding colony of the Institute of Physiology of the First Faculty of Medicine, Charles University, Prague. The experiment was performed in compliance with applicable guidelines for the use of laboratory animals – EU Council Directive 86/609/EEC. The animals were kept in boxes at 20–23 °C, using the standard 12-hour light/12-hour dark cycle. The animals received a normal diet and had water available *ad libitum*. The rats were divided in three groups. The control group (group-C, intact) included 6 rats; the experimental group (group-E, with the nerve transected on the left) included 12 rats; and the sham group (group-S, with the nerve prepared without transection) included 8 rats.

Transection of the inferior alveolar nerve

The surgery was performed under general anesthesia induced using intraperitoneal administration of thiopental 4 mg/100 g of rat weight. A microsurgical technique was used to approach and excise the nerve (used microscope: Carl Zeiss OPTON S4, Germany). An incision in the left face was used to expose the masseter muscle fascia, which was cut in the direction of muscle fascicles between the facial nerve and the parotid duct. After preparing the muscles, we reached the lateral part of the mandible at the place of its prominence (*tuberculum massetericum*). The bone crest (*crista masseterica*) was identified in the direction from the prominence to the condylar process (*processus condylaris*). Caudally from the prominence, we used a round dental milling cutter sized 1.2 mm (N 500.104.001.001.012 TC, Medin, a.s., Nové Město na Moravě) to remove a part of the bone and expose the neurovascular bundle in the range of 3 mm. The nerve was slightly pulled out from the mandibular canal and excised in the range of 3 mm. The neurovascular bundle was prepared using a microsurgical technique. This procedure enabled us to avoid causing any injury to blood vessels while excising the part of the nerve. The wound was rinsed with 1 ml of saline solution. Edges of the muscle were adapted using one non-absorbable suture. The same non-absorbable material was used to close the skin.

Animal killing and extraction of the molars

Four weeks later, the animals were weighted and killed by overdosing with thiopental using intraperitoneal administration. Individual molars (M1, M2, and M3) were gradually extracted from the mandible (on both sides). The teeth were mechanically cleaned and rinsed in *aqua pro injectione*.

Chemical analysis

The weighted amount of 10–20 mg of the dried samples of individual molars were inserted to 10 ml volumetric flasks; a value of 0.5 ml of concentrated HNO_3 was added; subsequently, the samples were dissolved by careful heating of the glass on the heating plate at approx. 100 °C. After cooling, deionized water was added to the mark of the volumetric flask. Blank samples were prepared for every series of 20 samples. The measurement quality was tested by analyzing the standard reference material (SRM 1400, Bone Ash, National Institute of Standards and Technology, Gaitersburg, MD). Differences between the measured and certified values were lower than the 10% RSD (relative standard deviation). All the acids used in the dissolution procedure were reagent grade (Merck, Darmstadt, Germany). Deionized water from MilliQPlus (Millipore, Billerica, MA) were used to prepare the solutions. The contents of Mg, Na, K, Ca, Zn, and Sr in the solutions were determined using inductively coupled plasma mass spectrometry (ICP MS, X Series II, Fisher Scientific, Gmbh, Bremen, Germany) under the following conditions: ICP 1350 W, “peak jump” measurement mode, measurement time 3×50 s, ion optics parameters optimized

with Ge, Rh, and Re 20 µg/l solutions (Astasol, Analytika, Czech Republic), gas flows 13.5 l/min (cooling), 0.7 l/min (auxiliary), 0.65 l/min (nebulizer). Measured isotopes of ^{72}Ge, ^{103}Rh, ^{185}Re, were used as internal standards.

Statistical analysis

1) The comparison of mean weight increase of the animals after 4 weeks among the groups was done using the Kruskal-Wallis test.
2) Respecting the skewed distribution and non-constant variance in most dependent variables, these were transformed by power transformations to data symmetry and homoscedasticity prior further processing (Meloun et al., 2000). The homogeneity and distribution of the transformed data and residuals was checked by residual analysis as described elsewhere (Meloun et al., 2002, 2004). The model consisted of Subject factor explaining inter-individual variability, between-subject factor Group (control [C], experimental [E], sham [S]), within-subject factors Location (three sites were investigated in animal such as M1, M2, and M3) and factor Side (right [R] vs. left [L]), and all corresponding interaction between the factors except of the subject factor. For instance, significant Group×Location interaction indicates that the Group factor significantly influences the arrangement of differences between location of sampling sites. Statistical software Statgraphics Centurion, version 18 from Statgraphics Technologies, Inc. (The Plains, Virginia, USA) was used for the statistical analysis.

The null hypotheses in all factors and all possible between-factor interactions were tested. However, the primary questions were associated with null hypotheses for the interactions as follows: factor difference between groups, Group×Location, Side×Group, Side×Location, and Side×Group×Location.

Results

Change in animal weight

No statistically significant differences in weight gain of the animals were shown between individual groups during the observation period (4 weeks).

Analyzed elements

Six elements were analyzed in all groups: Mg, Na, K, Ca, Zn, and Sr.

Change in element contents in mandibular molars (M1–3)

The content of **Mg** in group-C is lower compared to group-E and group-S. At the same time, there is a difference between group-E and group-S. A difference between the left and right sides was observed only in group-S (Figure 1).

For **Na**, the content is lower in group-E and group-S compared to group-C. In group-E, the arrangement of the left and right sides differed from group-C and group-S (Figure 2).

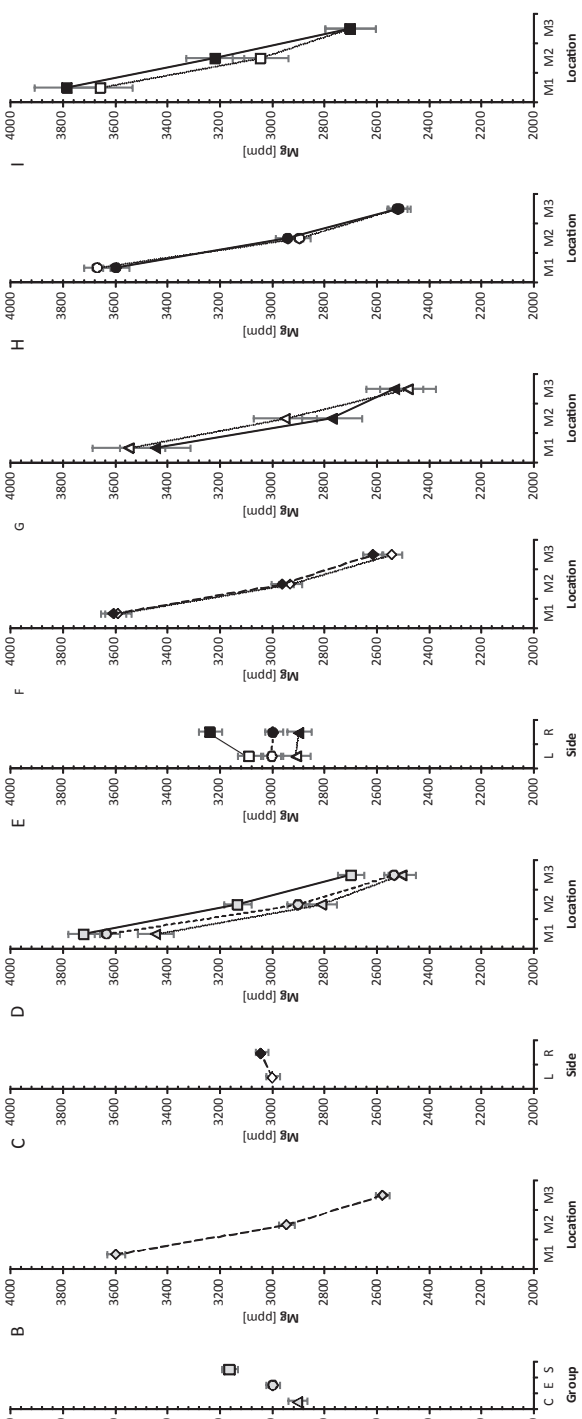

Figure 1 – The relationships between concentrations of Mg (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The model consisted of Subject factor explaining inter-individual variability, between-subject factor Group (control [C], experimental [E], sham group [S]), within-subject factors Location (three sites were investigated in animal such as M1, M2, and M3) and factor Side (right [R] vs. left [L]), and all corresponding interaction between the factors except of the subject factor. F represents the Fisher's statistic and p designates statistical significance for the factors and interaction. The symbols with error bars represent re-transformed means with their 95% confidence intervals (triangles, circles, and squares symbolize C, E, and S group, respectively, while the diamonds the summary for all groups). The full and empty symbols represent right and left side of sampling, respectively, while the grey ones the summary for both sides. The 95% confidence intervals are computed using the least significant difference multiple comparisons (p<0.05). The confidence intervals, which do not overlap each other, denote significant difference between the respective subgroup means. Statistical software Statgraphics Centurion, version 18 from Statgraphics Technologies, Inc. (The Plains, Virginia, USA) was used for the statistical analysis.

All – Group: F=32.1, p<0.001 (Panel A); Location: F=534.7, p<0.001 (Panel B); Side: F=2.7, p=0.101 (Panel C); Group×Location: F=1.9, p=0.119 (Panel D); Group×Side: F=4.1, p=0.019 (Panel E); Location×Side: F=0.6, p=0.554 (Panel F); Group×Location×Side: F=0.4, p=0.81; Subj(Group): F=31.8, p<0.001.

Group C – Location: F=72, p<0.001; Side: F=1.1, p=0.296; Location×Side: F=1.1, p=0.353 (Panel G); Subj: F=14.7, p<0.001.

Group E – Location: F=626.2, p<0.001; Side: F=0.1, p=0.781; Location×Side: F=1.5, p=0.23 (Panel H); Subj: F=59.2, p<0.001.

Group S – Location: F=89.4, p<0.001; Side: F=2.4, p=0.133; Location×Side: F=0.7, p=0.507 (Panel I); Subj: F=15.1, p<0.001.

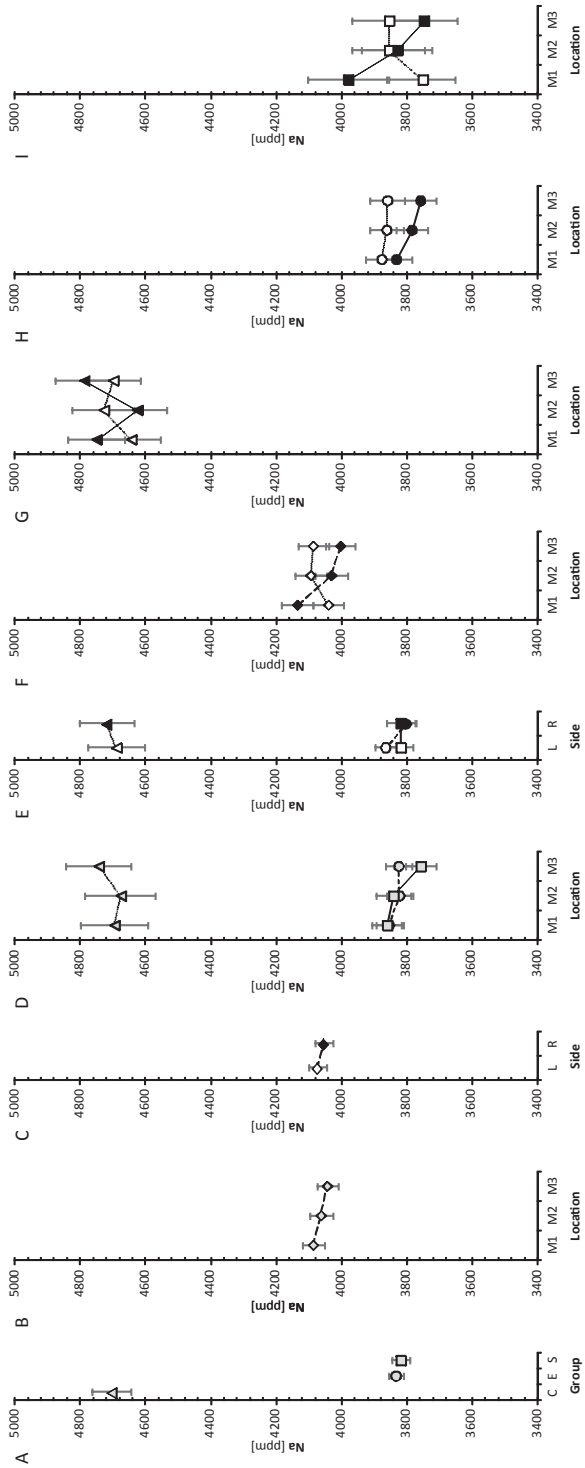

Figure 2 – The relationships between concentrations of Na (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The drawings and symbols are the same as for Figure 1.
All – Group: F=297.1, p<0.001 (Panel A); Location: F=0.8, p=0.441 (Panel B); Side: F=0.4, p=0.513 (Panel C); Group×Location: F=1.1, p=0.382 (Panel D); Group×Side: F=1.2, p=0.295 (Panel E); Location×Side: F=4.3, p=0.017 (Panel F); Group×Location×Side: F=3.1, p=0.019; Subj(Group): F=28.3, p<0.001.
Group C – Location: F=0.7, p=0.531; Side: F=0.3, p=0.57; Location×Side: F=1.8, p=0.197 (Panel G); Subj: F=89.5, p<0.001.
Group E – Location: F=0.9, p=0.406; Side: F=6.7, p=0.013; Location×Side: F=0.4, p=0.706 (Panel H); Subj: F=28.8, p<0.001.
Group S – Location: F=0.3, p=0.714; Side: F=0.2, p=0.638; Location×Side: F=2.6, p=0.086 (Panel I); Subj: F=13.9, p<0.001.

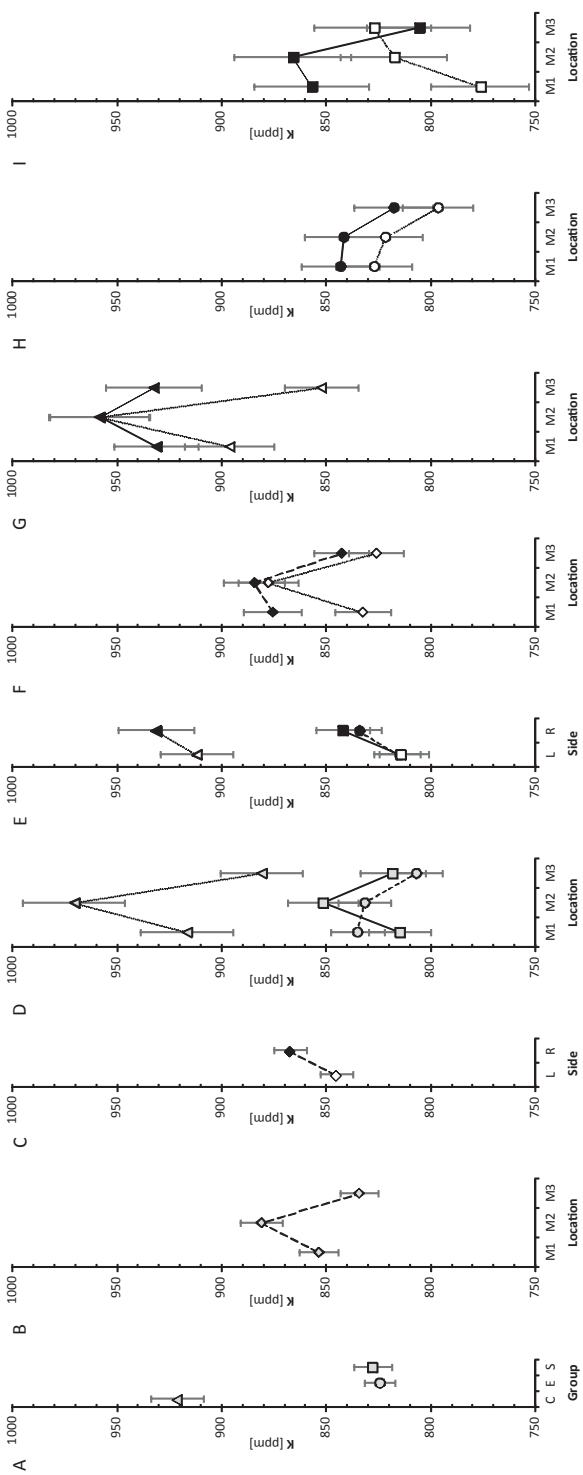

Figure 3 – The relationships between concentrations of K (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The drawings and symbols are the same as for Figure 1.
All – Group: F=52.4, p<0.001 (Panel A); Location: F=11.6, p<0.001 (Panel B); Side: F=7.8, p=0.006 (Panel C); Grou×Location: F=2.4, p=0.058 (Panel D); Group×Side: F=0.2, p=0.822 (Panel E); Location×Side: F=1.9, p=0.154 (Panel F); Group×Location×Side: F=3.5, p=0.01; Subj(Group): F=33.8, p<0.001.
Group C – Location: F=10.8, p<0.001; Side: F=10.6, p=0.004; Location×Side: F=4.3, p=0.028 (Panel G); Subj: F=105.3, p<0.001.
Group E – Location: F=2.9, p=0.065; Side: F=3.4, p=0.072; Location×Side: F=0, p=0.973 (Panel H); Subj: F=44, p<0.001.
Group S – Location: F=1.3, p=0.281; Side: F=5.8, p=0.022; Location×Side: F=4.2, p=0.024 (Panel I); Subj: F=4.3, p=0.002.

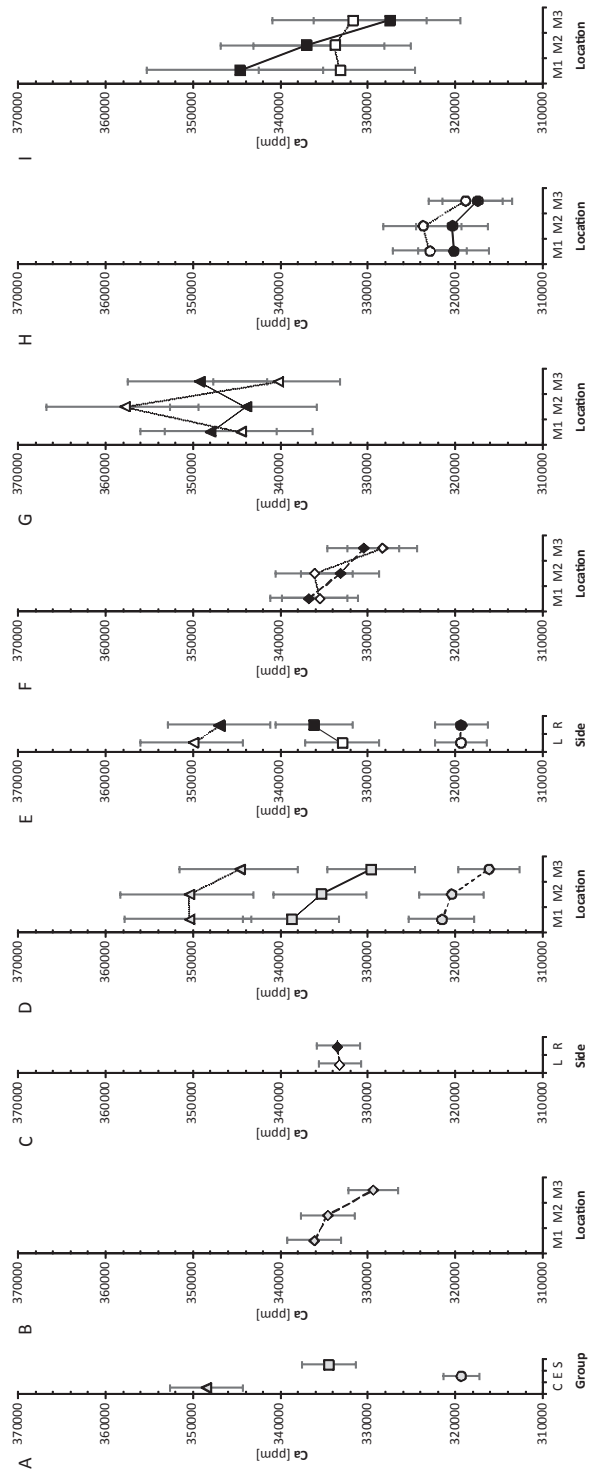

Figure 4 – The relationships between concentrations of Ca (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The drawings and symbols are the same as for Figure 1.
All – Group: F=48.3, p<0.001 (Panel A); Location: F=2.7, p=0.069 (Panel B); Side: F=0, p=0.942 (Panel C); Group×Location: F=0.1, p=0.988 (Panel D); Group×Side: F=0.4, p=0.669 (Panel E); Location×Side: F=0.4, p=0.678 (Panel F); Group×Location × Side: F=1.2, p=0.315; Subj(Group): F=9.3, p<0.001. Group C – Location: F=0.6, p=0.545; Side: F=0, p=0.967; Location×Side: F=2.3, p=0.126 (Panel G); Subj: F=11.3, p<0.001. Group E – Location: F=1, p=0.36; Side: F=1.1, p=0.311; Location×Side: F=0.1, p=0.949 (Panel H); Subj: F=7.9, p<0.001. Group S – Location: F=1.1, p=0.35; Side: F=0.4, p=0.532; Location×Side: F=0.8, p=0.481 (Panel I); Subj: F=14.3, p<0.001.

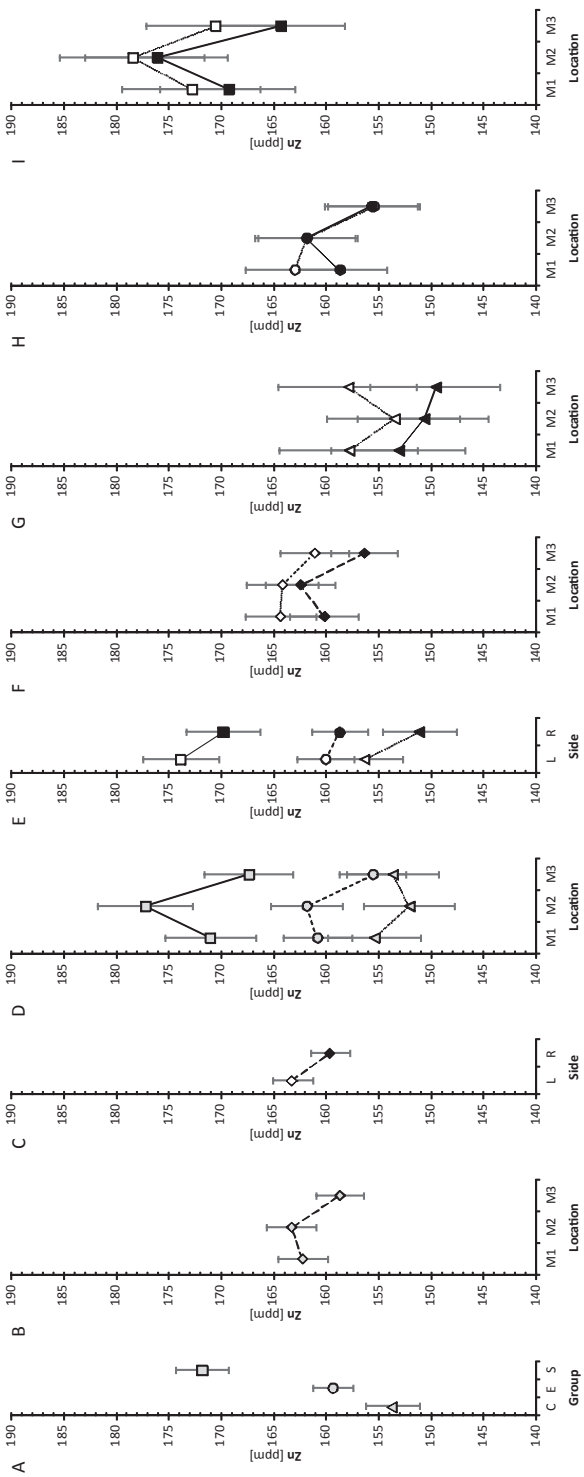

Figure 5 – The relationships between concentrations of Zn (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The drawings and symbols are the same as for Figure 1.
All – Group: F=27.8, p<0.001 (Panel A); Location: F=2.1, p=0.126 (Panel B); Side: F=3.5, p=0.065 (Panel C); Group×Location: F=1, p=0.431 (Panel D); Group×Side: F=0.4, p=0.651 (Panel E); Location×Side: F=0.2, p=0.785 (Panel F); Group×Location×Side: F=0.2, p=0.941; Subj(Group): F=16.1, p<0.001.
Group C – Location: F=0.3, p=0.751; Side: F=2.2, p=0.153; Location×Side: F=0.2, p=0.821 (Panel G); Subj: F=9.1, p<0.001.
Group E – Location: F=2.2, p=0.119; Side: F=0.3, p=0.61; Location×Side: F=0.3, p=0.738 (Panel H); Subj: F=19.8, p<0.001.
Group S – Location: F=2.4, p=0.109; Side: F=1.2, p=0.282; Location×Side: F=0.1, p=0.895 (Panel I); Subj: F=15.5, p<0.001.

Figure 6 – The relationships between concentrations of Sr (ppm) in groups, location of sampling sites, and side of sampling were evaluated using ANOVA model. The drawings and symbols are the same as for Figure 1.
All – Group: F=246.7, p<0.001 (Panel A); Location: F=73.3, p<0.001 (Panel B); Side: F=0.8, p=0.369 (Panel C); Group×Location: F=0.7, p=0.614 (Panel D); Group×Side: F=1.6, p=0.208 (Panel E); Location×Side: F=0.4, p=0.704 (Panel F); Group×Location×Side: F=1.2, p=0.336; Subj(Group): F=36.1, p<0.001.
Group C – Location: F=47.4, p<0.001; Side: F=0.6, p=0.434; Location×Side: F=1.2, p=0.32 (Panel G); Subj: F=3.4, p=0.018.
Group E – Location: F=34.2, p<0.001; Side: F=0, p=0.917; Location×Side: F=0.2, p=0.791 (Panel H); Subj: F=24, p<0.001.
Group S – Location: F=14.7, p<0.001; Side: F=2.1, p=0.161; Location×Side: F=1.5, p=0.228 (Panel I); Subj: F=54.3, p<0.001.

For **K**, the content is lower in group-E and group-S compared to group-C. In group-C, a difference was observed between the left and right sides in M3; in group-S, a difference was observed in MI. No such differences between the sides were shown for group-E (Figure 3).

For **Ca**, the content is lower in group-E and group-S compared to group-C. At the same time, there is a difference between group-E and group-S. No differences were shown between individual molars (M1–3) (Figure 4).

The content of **Zn** was higher in group-E and group-S compared to group-C. At the same time, a difference was observed between group-E and group-S (Figure 5).

For **Sr**, the content is lower in group-E and group-S. At the same time, there is a difference between group-E and group-S (Figure 6).

Discussion

We believe that the finding of a neurogenic effect on tooth tissue is important (Jacobsen and Heyeraas, 1996; Fristad, 1997; Byers et al., 2003; Berkovitz, 2016). We expected to observe substantial changes in element contents on the operated side in the study. However, as shown by the results, similar changes occur also on the opposite side of the mandible.

The subsiding of neuralgia after a surgery on the opposite side was documented by Kunc (1976). As found by this author, vertical nucleotomy affects also the contralateral second neuron, which, past the crossing point, runs not far from the hilum of the nucleus caudalis (Kunc, 1976). This fact explains our results (change in element contents on the contralateral side, as well) – although the IAN was transected only on one side, the contralateral nerve ending became affected, as well.

As follows from the study of Travers (2015), the spinal trigeminal nucleus affects afferentation of the ipsilateral trigeminal motor nucleus, and via connections from the reticular formation to the hypothalamus and up to the cerebral cortex it affects the contralateral region supplied by the trigeminal nerve. As follows from the above mentioned study, the transection of IAN causes changes in the spinal trigeminal nucleus and affects the other side of the mandible, as well.

These facts can have an impact on mastication of the animal and thus on mandibular load. As reported by various authors, the loading of the mandible affects bone mineralization, which is different in various parts of the mandible (Tanaka et al., 2007; de Jong et al., 2013; Hichijo et al., 2015).

We believe that these effects are involved in the change of element contents in the mandibular molars, and particularly, in concurrent changes of element contents on both sides of the mandible as shown in our study.

As reported by Jacobsen and Heyeraas (1996) in their study, the transection of IAN resulted in an almost complete loss of immunoreactive fibrils in the pulp and in a reduction of dentin production compared to the control group.

We did not show any statistically significant change in the weight of the animals during the 4-week observation period. We thus do not expect an effect of food intake on the contents of chemical elements in the molars.

Given that no description of effects of transectioning this nerve on chemical elements in teeth is found in available literature, it is difficult to perform any comparison to previous studies.

Statistically significant differences between the control and experimental groups and a difference between the experimental and sham groups support the concept that the transection of the nerve actually has an effect on the chemical elements. If no difference is found between the experimental and sham groups but a difference is found between both of these groups and the control group, such results indicate an effect of the surgery itself.

The transection of the nerve causes a reduction of the contents of the following elements in mandibular molars: Ca, and Sr. Additionally, an increase in the contents of Mg and Zn were caused. Furthermore, the transection caused a difference arrangement of both sides in Na.

The surgery caused a decrease in the contents of Na and K in the experimental and sham group. Furthermore, the difference in K in M3 between the left and right sides disappeared due to the surgery.

As reported by Naftel et al. (1999) in relation to the nerve supply of the molars in the rat, branches of the IAN innervate the M1 and anterior part of the M2. Distal part of the M2 and M3 innervate by branch of the lingual nerve.

The transection of the IAN caused a change in the inorganic component of the MI and M2, but also of the M3. Our experience and literary date do not explain this fact.

Conclusion

Our results have confirmed the hypothesis of IAN transection having an effect on the inorganic components in mandibular molars in the rat. This means that changes in mandibular molars in humans can be expected upon IAN transection, meaning that the nervous system is involved. Principal changes in the inorganic component of molars should be expected after an injury to IAN associated with maxillofacial surgery procedures, trauma or planned transection of the nerve in mandibular osteotomy or resection procedures. All consequences of these changes should thus be taken into account as regards the prognosis of individual molars in the mandible. We assume that a change of the mineralization of teeth can affect, for example, the occurrence of caries. As follows from our study, these changes involve molars on both sides of the mandible. Additionally, surgical approach to the nerve itself has an impact on mineralization of the teeth, as indicated by the study.

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