Author’s response to reviews

Title: Chronodentistry: The role & potential of molecular clocks in oral medicine

Authors:

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Version: 1 Date: 01 Dec 2019

Author’s response to reviews:

Submission of the revised manuscript "Chronodentistry: The role & potential of molecular clocks in oral medicine"

Dear Ladies and Gentlemen,

Please find attached the revised version of the manuscript "Chronodentistry: The role & potential of molecular clocks in oral medicine" by the authors Klara Janjić and Hermann Agis.

The manuscript has been amended to the comments of the reviewers; a point-by-point response to each comment can be found below and changes within the manuscript are highlighted by the “track change mode”.

We kindly request the evaluation of our commissioned review for publication in the renowned BMC Oral Health journal.

Sincerely yours,

Hermann Agis, PhD, on behalf of the authors

Point-by-point response letter

Reviewer 1
Comment 1 of reviewer 1: “Chronodentistry is an interesting and innovative review topics, that is well focussed. Although it is rather well documented, I feel its structure deserves some reappraisal while additional references and work should be discussed and cited. Reports regarding rodents and humans should be clearly separated.”

Response to comment 1 of reviewer 1: Structure and references have been changed and added following the comments of the reviewers. Following this comment and comment 5 of reviewer 2 we structured each chapter into sub-chapters entitled “Biological aspects” and “Clinical aspects”. These sub-chapters already separate most rodent and human findings. For a definite separation, the notation of genes and proteins follow the guidelines for formatting gene and protein names (GENE and PROTEIN for humans and Gene and PROTEIN for rodents). Additionally, we created a table (Table 1) listing all core findings for each chapter, including the respective research model and species. We hope that these changes now provide a clear distinction between rodent and human findings for the reader.

Comment 2 of reviewer 1: “As this is a review rather than an original report, the questions regarding Methods, Controls and Statistics are not relevant. I can assess all three but not in this manuscript.”

Response to comment 2 of reviewer 1: We thank reviewer 1 for this important comment. Information on Methods, Controls and Statistics were removed throughout the manuscript. Although, in the Discussion section we decided to leave a few phrases about methodology in chronobiology, since this information is essential for the interpretation of publications from this field and might not be common knowledge for professionals from other fields than chronobiology.

Comment 3 of reviewer 1: “A comprehensive view of the circadian timing system (CTS) would help the reader understand the links between the brain pacemaker (SCN) that both measures light and darkness and coordinates an array of physiological rhythms, including sleep, and the peripheral clocks, including those in the oral cavity, which you are addressing more specifically. Such systems approach will help you highlight the relevance of a functional CTS for chronodentistry over the 24 h, so that interventions can be timed to maximize efficacy and tolerability according to local molecular clocks. In contrast, CTS dysfunction, irrespective of its cause - genetic, lifestyle or other - can result in poor coordination of the oral cavity clocks, possibly resulting in abnormal development or local diseases, and requiring clock-targeted systemic or local treatments. In this respect the relevance of atypical lifestyles or poor circadian synchronisation during development for dentition could be discussed.”

Response to comment 3 of reviewer 1: We now emphasize in the Introduction section (lines 69 – 78, pages 2 - 3) how the circadian timing system can have positive or negative effects,
especially in the oral region and we also discuss (possible) relations between atypical lifestyles, circadian clock dysfunction and dentistry/tooth development. We thank the reviewer for this suggestion.

Comment 4 of reviewer 1: “Several statements such as "this tissue is able to produce the core components of the circadian clock" is not very sound and is repeated throughout in almost each subsection. You might want to say that "the core clock genes are expressed in all the tissues that are relevant for chronodentistry, including......" or something alike.”

Response to comment 4 of reviewer 1: We thank the reviewer for pointing this out and removed all the repetitive phrases of this kind throughout the manuscript. As suggested by the reviewer, we now only have a summarizing phrase in the beginning of the Discussion section (lines 315 – 317, page 13).

Comment 5 of reviewer 1: “There are several old works that deserve to be cited and updated regarding the circadian changes in tooth pain thresholds in humans (Reinberg, Pollmann), and more recent ones regarding the cell cycle and clock genes circadian expression in human oral mucosa (Bjarnason), and their implications for chronoradiotherapy (Bjarnason and others), as well as for chronochemotherapy of head and neck cancers (several Chinese papers).”

Response to comment 5 of reviewer 1: We thank reviewer 1 for these valuable suggestions and integrated proposed references in appropriate sections: pain sensation and analgesic treatment were added to the Endodontics section (lines 231 – 235, page 10) and the Orthodontics section (lines 309 – 312, page 13), cell cycle, chronoradiotherapy and chronochemotherapy were added to the Oral & maxillofacial surgery section.

Comment 6 of reviewer 1: “There is a need for comprehensive figures that summarize the main implications of circadian clocks for oral Health.”

Response to comment 6 of reviewer 1: As reviewer 2 suggested to add a table listing the literature that was used for this review, we created a table (Table 1) that summarizes all publications and their findings which contain findings on the circadian clock and dentistry or dental tissues. To our opinion a table provides a clearer arrangement to summarize all literature than a figure. If a graphical presentation is still required we are willing to implement a new figure.
Reviewer 2

“The authors describe in this narrative review the influence of the circadian clock on oral tissues. The topic is very interesting and clearly presented. Nevertheless, there are still some points that would be worth discussing.”

Comment 1 of reviewer 2: “Please change article type.”

Response to comment 1 of reviewer 2: Thank you for this important comment. We would apply this change if it would be possible to implement the change in the submission system. However, for the article type there was no option termed “Commissioned Review” or “Review” to choose. Therefore we now state the article type on the cover letter and the title page. We hope that the reviewer finds this applicable.

Comment 2 of reviewer 2: “I do not understand the sentence “The main….” from line 57-59. Please rewrite this sentence.”

Response to comment 2 of reviewer 2: The phrase has been rephrased and split into two phrases to present the content in a more understandable way to the readers from different backgrounds. (Introduction section, lines 59 – 62, page 3)

Comment 3 of reviewer 2: “In dentistry, the appearance and prevention of pain are of great interest for both the patient and the dentist. Please also discuss this important point.”

Response to comment 3 of reviewer 2: Indeed, pain sensation and analgesic treatment are highly interesting topics for chronotherapy. We thank both reviewers for adding this point which we now describe in the Endodontics section, lines 231 – 235, page 10 and the Orthodontics section, lines 309 – 312, page 13.

Comment 4 of reviewer 2: “Restorative Dentistry: please do not mix ameloblasts and odontoblasts.”

Response to comment 4 of reviewer 2: We thank reviewer 2 for this suggestion and separated content on ameloblasts and odontoblasts into separate paragraphs. (throughout Restorative Dentistry section)
Comment 5 of reviewer 2: “Please make a more structured distinction between the influence of circadian rhythm on tissue development/maturation and on tissue treatment.”

Response to comment 5 of reviewer 2: The content of each chapter has been sub-divided into “Biological aspects” and “Clinical aspects”. We think that these subtitles help to make a clear distinction between findings relevant to development or treatment, respectively.

Comment 6 of reviewer 2: “In endodontics the influence on pulp capping/pulp regeneration would be interesting to know.”

Response to comment 6 of reviewer 2: We agree that pulp capping and pulp regeneration are interesting in the context of circadian clocks. We added two references which are connected to this topic and discuss them in the Endodontics section (lines 221 – 228, page 10).

Comment 7 of reviewer 2: “Please check citation at line 192. Please also check the space before your citations.”

Response to comment 7 of reviewer 2: We thank reviewer 2 for careful proof reading of the references. We checked for correctness and formatting of the references and updated them within the manuscript and the reference list.

Comment 8 of reviewer 2: “Bruxism is not really part of orthodontics. Please change this.”

Response to comment 8 of reviewer 2: We realized that bruxism does not fit definitely into any of our sections. Therefore we moved the content on bruxism to the Discussion section (lines 346 – 349, page 15).

Comment 9 of reviewer 2: “Oral- and maxillofacial surgery seems to be most influenced (or investigated). Maybe this field should be described first.”

Response to comment 9 of reviewer 2: The chapter “Oral & maxillofacial surgery” has been moved to the first position of the chapters, directly after the Introduction section. Also in other parts of the manuscript as Abstract, Introduction and Conclusions it is mentioned first when listing or discussing the different chapters.
Comment 10 of reviewer 2: “The Conclusion is very long. Maybe it could be changed to a Discussion and a separate short Conclusion could be added.”

Response to comment 10 of reviewer 2: We agree that separate Discussion and Conclusion sections improve the readability of the manuscript. Since we could not find any clear statement in the submission guidelines on section titles for reviews, we followed this comment of reviewer 2 and divided the former “Conclusions” section into a “Discussion” and a “Conclusion” section.

Comment 11 of reviewer 2: “At authors contribution “study design” is written. Please describe the selection criteria for this review.”

Response to comment 11 of reviewer 2: The manuscript now contains the search criteria for literature used in this review in a separate section after the references heading “Appendix”.
(Appendix section, lines 605 – 614, page 23)

Comment 12 of reviewer 2: “Fig. 1: maybe “Zeitgeber” could be changed to the English word. Soft tissue seems to be more influenced by the circadian clock. It would be nice to reflect this in the figure”

Response to comment 12 of reviewer 2: Indeed, “zeitgeber” is an official technical term that is widely used in chronobiology and related fields. An official English equivalent does not exist. We now added this information in the figure legend for Figure 1 and Figure 3. Throughout the manuscript the term zeitgeber is written in italics to signalize that it is a technical term. Further, the tooth icon in Figure 1 now includes soft tissues and bone.

Comment 13 of reviewer 2: “Please also add a table describing the literature on which the review is based.”

Response to comment 13 of reviewer 2: We thank reviewer 2 for this suggestion. We created a table (Table 1) listing the literature that is connected to the circadian clock and dentistry, organized in columns for “Field of dentistry”, “Molecule/Target”, “Major finding”, “Study model”, “Species” and “Reference”.