Author's response to reviews

Title: An immunohistochemical study of the antinociceptive effect of calcitonin in ovariectomized rats

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Author's response to reviews: see over
Reviewer 1  Dear Dr. Milka Sekulic
Thank you for your comments.

Q1
-page 14, 9th line: "Our results suggest that repeated systemic injection...has an antinociceptive effect" - Since the authors did not show any behavioral results in this study, they should relate their immunohistochemical findings with the behavioral results of their previous or someone else results.

A1
Thank you for your comment.
The expression of c-Fos in the dorsal horn increased and the pain threshold decreased after formalin or yeast injection and skin incision. Administration of NSAIDs or anesthegia effects to improve pain threshold and inhibit c-Fos expression in the spinal cord (reference #36-39). The behavioral results correlate with the expression of c-Fos immunoreactivity which is induced by injection of formalin or yeast and skin incision. We have added this point to the discussion section. (page 14 line 10~14)

Q2
-page 14, 13th line-till the end of the paragraph: "Our results seems to be consistent with this mechanism, but conflict with it because..." The part of the discussion related to the possible serotoninergic mechanism of antinociceptive calcitonin action should be rephrased. The authors should make their points clear and easy for reader to follow (what are pros and cons?).

A2
Thank you for your comment. We agree with you. In order to avoid readers confusion, we have deleted this sentence.

Q3
-the manuscript has many typing errors that should be corrected
A3
Thank you for your comment. We have asked a English specialist to check this manuscript.

Q4
-please check the last sentence in the abstract (behavioral and electrophysiological study???)

A4
Thank you for your comment.
We have changed the sentence. (page 2 line 8~9)

Reviewer 2  Dear Dr. Morten Karsdal
Thank you for your comments.

Q1
Few minor things could be included in the discussion.
1) A discussion on the effects of calcitonin on pain observed in clinical trials og postmenopausal osteoporosis
2) A discussion of potential clinical benefits on pain effects of calcitonin. In particular in light of the proposed effects in osteoarthritis.
3) A discussion on the similarities and dissimilarities between the animmodel and the clinical pain observed in osteoporosis and osteoarthritis

Thank you for your important comments.
We have added the following part to the discussion section as per your suggestion. (page 14 line 15~page 15 line 10)
The c-Fos expression is related with the reaction of the formalin test but does not reflect the bone pain by postmenopausal osteoporosis in this study. There are studies that calcitonin has the effect of reducing bone pain associated with bone metabolic disorders, compression fracture, and osteoporosis. The bone pain induced by ovariectomy was not investigated in this study. In addition, the pain induced by the formalin test is quite different from the clinical situation and tissue damage is worse than the clinical situation. This is a limitation of this study,
however, calcitonin has the effect of inhibiting formalin-induced c-Fos expression which is a strong stimulant. Thereby, the results in this study show the benefit of calcitonin treatment. There are studies that show calcitonin has an effect on patients with osteoarthritis (OA) in the clinical trail and improves cartilage erosion in the experimental studies. Elderly people have possibility of developing both osteoporosis and OA. Furthermore, calcitonin provides benefits of improving osteoporosis itself, bone pain, hyperalgesia induced by postmenopausal condition and OA. Calcitonin may provide the benefit of improving symptoms various ways. In addition, clinical trials for calcitonin treatment on the different conditions of each disease are needed.