Author’s response to reviews

Title: Corticosterone mediates electroacupuncture-produced anti-edema in a rat model of inflammation

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Author’s response to reviews: see over
Dear Dr. Parkin:
Attended please find the revised manuscript MS # 1685510606135173, entitled "Corticosterone mediates electroacupuncture-produced anti-edema in a rat model of inflammation" by Li et al. We would like to express our cordial thanks to the editors and reviewers for their constructive comments. We have revised the manuscript carefully to incorporate their comments and suggestions. The following responses address the reviewers' point-by-point concerns and are reflected in the text.

Reply to reviewer #1

1. "Why the result of cortisol measurement is in %? Please explain."
   We present the data as percentage changes because that makes the results clearer and easier to read. (see page 8, Data Analysis section)

2. "Did you test the point specificity? Is it only effective for GB 30? Underneath this acupoint is sciatic nerve. Have you tried different acupoints that overlying on other nerves, such as some superficial nerves?"
   We did not test point specificity in this study because we tested it on the same model in our previous study (Lao et al. 2004). In that point-specificity study, EA at GB30 produced better anti-hyperalgesia than EA at acupoint Waiguan (the fifth acupoint on the Triple Energizer Meridian, TE 5) on the forepaw and at two non-specific points, an abdominal point and a point on the quadriceps opposite to GB30. Waiguan is located dorsally between the radius and ulna, 2 units (based on the standard acupuncture measurement of 12 units) above the transverse crease of the wrist. Underneath are the posterior interosseous nerve and the anterior interosseous nerve. (see page 7, Lines 4-11)

3. "How long does this EA effect last?"
   According to the corticosterone results, there was a significant difference between the EA and sham EA groups 5 hr after the CFA injection, that is, 3 h after the 2nd EA treatment. This indicates that EA effects on corticosterone may last at least 3 h. (see page 8, the last 2nd line)

4. "How much blood do you draw from the rat?"
   We drew 0.5 ml of blood at each of three time points, baseline and 2 h and 5 h post-CFA. (see page 5, paragraph 2, lines 7-8)

5. "Did you connect the electrodes from left to right? The EA electrodes better connected on ipsilateral side, do not pass current through heart"
   An acupuncture needle was inserted into GB 30 on each flank of the animal. Because the low stimulation intensity (3 mA) was applied at the lower part of the body, the current would be unlikely to pass through the heart. This bilateral connection has been used previously by our team and others with no adverse effects (Lao et al. 2001, 2004; Chang et al. 2006, Iwa et al. 2006). We also found, and reported, that bilateral
stimulation was more effective than unilateral stimulation in our animal model. Furthermore, this method of bilateral electrode connection is widely used clinically, and no known adverse effects have been reported (Lao et al. 2003; Macpherson et al. 2001, 2004). (See page 7 paragraph 2, lines 3-6)


Reply to reviewer #2

1. “In the manuscript, the author emphasized that there is no “observable signs of distress.” This is a very important point and the authors may want to further clarify whether EA stimulation intensity is the same for CFA and naïve rats. If this is the case as the authors assumed, then it is possible that the same stimulation intensity may produce different stress levels in CFA and naïve rats (CFA rats may be more sensitive to stimulation) Although stress levels might slightly differ and unlikely change the results, the authors may want to mention this possibility in their discussion.”

We used the same stimulation intensity for CFA-inflamed and naive rats in the present study. As we reported before, this intensity at acupoint GB30 did not change heart rate or blood pressure, both of which are stress response indicators, in CFA-inflamed rats. This indicates the EA procedure and acupuncture needle stimulation used do not induce significant stress responses. Further, sham EA did not increase plasma CORT level, which also demonstrates that the EA procedures used in our study have no stress effects. Therefore, although CFA-inflamed rats may be sensitive to stimulation (e.g. EA), we believe that the CORT level increase
in EA-treated CFA rats is not a general stress response. We have revised the related discussion. (see page 10, paragraph 2)

2. “For all figures, please clarify whether your data is presented as mean ± SD or mean ± SE.”
   All the data are presented as mean ± SE as indicated in the legends.

3. “The final sentence of the abstract seems too strong, as there is always a gap between animal studies and what actually happens in the clinics. Thus, the study can only “suggest” but not “demonstrate” that “EA effects differ in healthy subjects and in those with pathologies.” To be more accurate, the authors may want to modify the second half of the concluding sentence.”
   We have revised the related sentences in the abstract and the conclusion to read “suggest”.

Sincerely yours,

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