Author's response to reviews

Title: Sex differences underlying orofacial varicella zoster associated pain in rats

Authors:

Crystal Stinson (stinson@tamhsc.edu)

Mohong Deng (dengmohong@hotmail.com)

Michael Yee (MBY1@pitt.edu)

Larry Bellinger (lbellinger@tamhsc.edu)

Paul Kinchington (kinchingtonp@upmc.edu)

Phillip Kramer (pkramer@tamhsc.edu)

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Author's response to reviews:

Thank you for the review. The comments have improved the manuscript and are greatly appreciated.

Comment 1: Although a novel model of orofacial varicella zoster associated pain was established, the titled "A model of orofacial varicella zoster associated pain in male and female rats" seems to be not exact. Most experiments were centered around gender differences in orofacial varicella zoster associated pain. Therefore, proposed to change the title to "Sex differences underlying orofacial varicella zoster associated pain in rats.

Rebuttal: The title has been changed to "Sex differences underlying orofacial varicella zoster associated pain in rats"

Comment 2: Given this model the first time was established, it would be better to give more discussion. For example, post herpetic neuralgia (PHN) in patients lasts more than 3 months after the resolution of the skin lesions, but in this rat model, allodynia and hyperalgesia are 50 days or so.

Rebuttal: We have added some discussion on this dosage effect in the last paragraphs before the conclusion. It states, "Zoster-associated pain may last 30-90 days during the acute phase however, about 20-30% of individuals develop chronic pain (>90 days) termed post-herpetic

neuralgia (PHN), which may last months to years [6-8, 56, 57]. In males a VZV dose of 65,000 pfu/whisker pad resulted in a significant response for one week and a dose of 190,000 pfu/whisker pad resulted in a 7 week response. Assuming a linear relationship between dosage and response an injection of 300,000 pfu/whisker pad would result in a 12 week response. A 12 week or 90 day pain response is one of the diagnostic criteria for PHN [56]. Future studies investigating higher dosages could indicate that this model is applicable for studying the mechanisms resulting in the development of PHN."

Comment 3: The subtitle "Post-menopausal women report greater herpes zoster associated pain than men" in the result possibly causes misunderstanding. Can't use the words of "women" and "men", as experiments are not performed on patients.

Rebuttal: the subtitle has been edited to state, "Pain was reduced in male rats versus female rats in a post-menopausal state"

Comment 4: The following articles may be useful for your mechanism discussion .

"Estrogen in the Anterior Cingulate Cortex Contributes to Pain-Related Aversion" published in Cerebral Cortex. doi:10.1093/cercor/bhs201: 1-14

"Involvement of Estrogen in Rapid Pain Modulation in the Rat Spinal Cord" in Neurochem Res DOI 10.1007/s11064-012-0859-1

Rebuttal: The discussion has been expanded to state: "This data is consistent with the nociceptive response in an inflammatory TMJ model where rats given a diestrus level of estradiol (low) had a greater nociceptive response in comparison to rats given a proestrus dose of estradiol (high) [48]. Mechanistically estradiol has been shown to alter the pain response through G-protein signaling [49]. Moreover, estradiol utilizes G-protein signaling to alter the nociceptive response by changing the responsiveness of N-methyl-D-aspartic acid (NMDA) receptors and by enhancing dendritic spine growth [50]. Although the mechanism is unclear as to why the nociceptive response was higher in females this animal model can be used to explore the mechanisms contributing to the observed sex difference."