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Response to Caro and Winter

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We thank Drs. Caro and Winter for their comments about our article showing diminished intraepidermal nerve fiber density (IENFD) in rats infused with a compound that raises central nervous system (CNS) glutamate levels.[2] They raise a number of thoughtful concerns about our results, which we respond to below. However, before that, we would like to address the overall interpretation of our study. The authors seem to have misinterpreted the phrase proof-of-concept in our title: "They purport that their findings represent a 'proof of [this] concept." Proof-of-concept does not mean evidence that a hypothesis should be accepted as definitive, but rather evidence that an experimental paradigm is feasible, and that the data are generally supportive of a hypothesis. Of course, we do not feel that this study proves that the decreased IENFD we noted was solely due to increased CNS glutamate, and we agree that additional studies are clearly warranted. We presented these preliminary findings because we believe this model has the potential to address the question of causality in the well-established link between fibromyalgia and IENFD. This is why we provided every data point collected in the experiment, including those from an animal where the surgical procedure failed to produce bilateral infusions into the insula. We used language throughout indicating that the results should be viewed as preliminary. We noted the small sample size as a limitation and called for replication in a larger sample that also includes female animals.

Why did we conduct such an experiment and present our results despite the acknowledged limitations? Our impression of the rapidly expanding literature on fibromyalgia and IENFD is that a number of researchers are preparing to make an entirely unwarranted leap from the observation that IENFD and fibromyalgia are associated with one another to the conclusion that IENFD causes fibromyalgia. To the best of our knowledge, not a single piece of preclinical or clinical data supports this conclusion: no prospective studies exist showing that IENFD is prospectively associated with new-onset fibromyalgia, and no animal models show that inducing IENFD causes multifocal pain, fatigue, disordered sleep, and cognitive dysfunction to develop. Before researchers and clinicians begin attempting to diagnose or treat fibromyalgia on the basis of IENFD, we implore them to consider alternative hypotheses.

We agree with many of the methodological issues raised by Caro and Winter. Their major criticism is that the craniotomy procedure may act as a confound, itself inducing a reduction in IENFD. We agree. In fact, the group of animals that underwent craniotomy with Ringer's infusions into the CNS had lower IENFD than naive animals. They are also quite correct that statistical inference is difficult with small groups and require fairly large effects to be detectable. Their focus on a lack of statistically significant findings is a bit puzzling; because by this logic, the fact that the group of Ringer's treated animals was not statistically different from naive animals in IENFD would seem to argue against the concern that craniotomy itself produces changes in IENFD.

We of course did include a control group of animals that underwent craniotomy to determine whether there are statistically significant differences in IENFD between animals administered with Ringer's alone and those also treated with PDC. We suggest that the remedy to this concern is a larger sample size to accommodate such a comparison—exactly what we originally suggested in the limitations section of the article.

We propose that our study provides intriguing preliminary data that the subtle changes in IENFD that are sometimes referred to as small fiber neuropathy in humans may not be a primary peripheral phenomenon but instead could be secondary to disturbances in the CNS, whether from increased glutamate levels, trauma, or any other myriad of factors. A reduction in IENFD is not necessarily evidence of neuropathy, nor a source of pain. As we have noted previously, these changes are nonspecific and have now been noted in scores of medical conditions, including most chronic pain states where this issue has been examined.[1] There is no evidence at present that suggests these changes are causing pain or should be a therapeutic target in any chronic pain state, any more so than the multitude or other commonly identified epiphenomenon that can be identified in chronic pain patients that are incidental findings (eg, bulging discs or osteophytes) or due to the chronic pain rather than the cause (eg, vitamin D deficiency).

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Disclosures

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