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We thank the three reviewers for their insightful and enriching comments on our Focus Article,[1] and feel encouraged to see that there are more agreements than divergences between their views and ours.

First, two of the Commentaries support the use of stomatodynia instead of burning mouth syndrome, while no objection was expressed in the third Commentary.

Second, there seems to be a consensus for a need to elucidate the mechanisms by which hormonal and neuroendocrine dysregulations induce local changes associated with stomatodynia. We are fully aware that the associations between stomatodynia and hormonal levels, and between stomatodynia and depression/stress disorders, are not new concepts. However, no theory has ever been proposed to reconcile the above phenomena.

Our hypothesis provides some insight into the possible missing link, by emphasizing the potential role of neurosteroids in the pathophysiology of stomatodynia. We propose the neurodegeneration associated with the drastic decline of neurosteroids following the concomitant falls of gonadal and adrenal steroids as a possible mechanism for the disorder. Several questions need to be addressed here.

Drs Eliav and Nasri-Heir[2] raised the issue as to why this would occur only in the oral cavity and not in other organs, while steroid dysregulation is a generalized condition. While it is difficult to fully explain why some disorders affect certain body sites but not others and why different subjects develop different disorders in response to similar severe physical and psychological stresses, the very restricted location of the symptoms in some areas of the oral mucosa in stomatodynia patients suggests that the involvement of hormonal steroids exclusively mediated through the bloodstream is unlikely. On the other hand, there is compelling evidence that neurosteroids can act locally as autocrine and paracrine messengers to locally influence neuronal activity. This has the advantage of limiting the steroid activity to the restricted body regions where the synthesizing cells are located and points to the site-specific feature of the action of neuroactive steroids. As suggested by Dr El-Etr,[3] the role of local neurosteroids can be challenged with clinical trials that evaluate the efficacy of topical application of neuroactive steroids or stimulation of local neurosteroidogenesis in the management of stomatodynia. Dr El-Etr suggested trials using topical neuroprotective, trophic, and antinociceptive neuroactive compounds such as progesterone and allopregnalone. In addition, 17 beta estradiol, which is largely synthetized in peripheral tissues, and dehydroepiandrosterone (DHEA), which is a neurosteroid precursor synthetized in both adrenal and peripheral tissues, are also good candidates. Dr El-Etr also raised the possibility that stomatodynia symptoms are restricted to regions which are in contact with saliva and thus, subjected to cortisol toxicity. The higher density of taste buds in stomatodynia patients, and the potential of greater loss of inhibition, as developed by Dr Zakrewska,[4] can be cited as more support for the hypothesis linking steroid-induced neuropathic changes with the local symptoms in the tongue.

Third, as for the question of why the symptoms cannot be reversed with systemic replacement therapy in all patients, the timing of therapy initiation may be a determinant, since neural damage is less likely to respond to treatment once the persistent insult has long been established and neurodegeneration has become irreversible. It is also important to note that some synthetic steroids used for hormonal supplementation cannot be metabolized into neurosteroids. Also, the steroid family is large and complex, with compounds interacting with and sometimes antagonizing each other. For example, the local production in neural tissues of the active metabolites of DHEA may oppose, via a paracrine mechanism, a deleterious effect induced by glucocorticoids. The change in the relative composition of the neurosteroid precursors mixture during hormonal therapy may alter the interactions among neurosteroids through receptor binding or metabolic pathways. This in turn may result in different effects on central and peripheral nervous tissues.

Fourth, our hypothesis is not exclusive of other possible mechanisms: glucose levels or damage to small blood vessels as Drs Eliav and Nasri-Heir pointed out or, as Dr Zakrewska suggested, complex

interactions between neural and endocrine systems, genetics, psychosocial, and environmental factors that make the individual more at risk for a particular disease. As for other chronic pain or functional disorders, these complex scenarios in any combination may hold the answer to questions such as why some individuals with steroid depletion do not develop stomatodynia.

We are pleased to see that our Focus Article has triggered interests for more research to elucidate the pathophysiology of stomatodynia. Whether future studies will focus on our hypothesis or others that were suggested by our reviewers, we hope that the results obtained for stomatodynia will also shed light on the pathophysiology of other functional disorders.

References

1. Woda A, Dao T, Grémeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:202–210.
2. Eliav E, Nasri-Heir C. Critical commentary on focus article: Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:214–215.
3. El-Etr M. Critical commentary on focus article: Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:216–218.
4. Zakrzewska JM. Critical commentary on focus article: Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:211–213.