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Activation of the migraine pain pathway by cortical spreading depression: Do we need more evidence?

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Dear Sir

We read with great interest the recent paper by Fioravanti et al. entitled “Evaluation of cutaneous allodynia following induction of cortical spreading depression in freely moving rats” published in a recent issue of *Cephalalgia* (1). In this paper the authors suggest that “cortical spreading depression (CSD) alone is not sufficient to lead to sustained activation of the trigeminal system that is likely to require to established cutaneous allodynia, at least in normal animals”. This conclusion was supported by two sets of experimental observations in which induction of CSD did not lead to increased c-fos expression in spinal trigeminal nucleus or the development of cutaneous allodynia in awake, freely moving rats.

This paper brings up a critically important yet unanswered question: Can an episode of CSD promote activation of the meningeal nociceptors that is sufficient to elicit headache? In their paper, Fioravanti et al. suggest that the lack of increase in dorsal horn c-fos expression and the absence of cephalic allodynia after CSD are likely to indicate insufficient amount of neural traffic in intracranial meningeal afferents and therefore the possibility that CSD itself may not be a sufficient noxious stimulus that can lead to migraine headache.

In an effort to answer part of this question, we showed recently using a rat model that CSD leads to a persistent activation of more than 50% of meningeal nociceptors and trigeminovascular neurons in the spinal trigeminal nucleus (2,3). We thus concluded that CSD can activate peripheral and central components of the trigeminovascular pathway (i.e. the migraine pain pathway). Because this answer does not allow us to conclude with certainty that activation of meningeal nociceptors and central trigeminovascular neurons is sufficient for eliciting the perception of headache in patients, the need to answer the question – how much ongoing activity in meningeal nociceptors is required to induce headache – remains high. In the absence of such information, one must be cautious in suggesting that low level of activity in a small number of nociceptors may be combined to a neural signal that is insufficient for generating pain perception. This point is further supported by clinical psychophysical studies which showed that induction of very few (single at times) action potentials in few nociceptors (using microneurography techniques) were sufficient to elicit the perception of pain in human subjects (4,5).

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Because a single CSD can evoke prolonged activation of meningeal nociceptors, one must ask why Fioravanti et al. could not detect an increase in dorsal horn c-fos following the induction of CSD? Should the lack of increase in dorsal horn c-fos expression serve as an indication of a lack of activation of meningeal nociceptors? Theoretically yes, however one must realize the limitation of the c-fos technique in pain studies as the minimal level of nociceptor activation (i.e. rate, duration and number of active nociceptors) that can yield unequivocal increase in dorsal horn c-fos expression above baseline values remained undefined. Furthermore, although dorsal horn fos expression is stimulus-dependent, the stimuli needed to evoke a measurable increase in fos expression often exceed pain threshold levels and are not closely correlated with pain behavior (6). Examining changes in dorsal horn fos expression following activation of nociceptors that innervate deep tissues, such as the meninges, poses a particular challenge because of the increased background level of fos resulting from the surgery needed to allow for the afferents' stimulation (7). In the study by Fioravanti et al. (1), as well as other studies that performed craniotomy, the increased background was likely due to the meningeal trauma evoked by the craniotomy (8). Taken together, one must be careful in concluding that the level of meningeal nociceptors' ongoing activity evoked in response to a single CSD, as observed using electrophysiological recordings, is insufficient to elicit the sensation of headache in humans.

Similarly, should the lack of cephalic allodynia be considered as an indication of insufficient nociceptive traffic that is incapable of promoting headache? Previous studies indicate that a strong stimulation of meningeal nociceptors using a combination of inflammatory mediators can give rise to central sensitization (9) and its behavioral correlate, cephalic allodynia (10,11). Cortical KCl administration elicits CSD and causes a brief, high-frequency burst of action potential in meningeal nociceptors (3). As shown by Fioravanti et al., this stimulus can lead to cephalic allodynia. Because CSD evoked by pin prick stimulation alone did not promote cephalic allodynia, the authors concluded that the neuronal traffic following CSD is not sufficient to promote the allodynia. As with the c-fos studies, it remains unclear what is the level of meningeal nociceptor activation that is actually required for the genesis of headache vis a vis the development of cephalic allodynia. In the case of the study of Fioravanti et al. it is interesting to note that the pronounced activation of trigeminal dorsal neurons seen in animals not exposed to CSD (as detected by c-fos), which likely resulted from the surgery performed prior to the experiments, also did not lead to a detectable cephalic allodynia. Clinical studies have shown that only 60–70% of migraine attacks lead to allodynia (12,13), suggesting that meningeal nociceptor activation does not always lead to central sensitization and the ensuing allodynia. In our opinion, it is even less likely to develop during the first migraine aura attacks as the propensity to develop migraine-related allodynia tends to increase with the number of attacks (13).

In conclusion, despite the frequent use of c-fos and the increasing utilization of behavioral sensory testing and measurement of allodynia in headache research, one must ponder the suitability of these methods to detect increased nociceptive traffic that can lead to headache, in particular in cases where there is direct electrophysiological evidence for persistent meningeal nociceptor activation. Preclinical headache research will benefit tremendously from the development of more sensitive methods that will be able to examine migraine headache equivalency in animal models. In addition to the cardinal role of electrophysiological recordings, more attention should be given to establishing complex behavioral tests that can detect some of the related symptoms of migraine, for example photophobia.

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