EDITORIAL

Too Much of a Good Thing? Brain Hyper Excitability and Migraine

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The pathophysiology of migraine remains an enigma, but more knowledge is steadily being added to our understanding of this very common neurological disorder. The more basic research that is done, the more there seems to be "abnormal" in the migraine brain, or at least different from the brains of those without migraine. A recent review emphasized that migraine may be primarily a disorder of perception, in that sensory inputs to the brain are not perceived normally[1]. Thus pain is felt when there "should" be none, and normal light inputs to the retina are perceived as painful.

It has been known for a long time that the migraine brain shows physiological differences from the usual. The most obvious of these differences and perhaps the longest studied is the increased susceptibility of the cerebral cortex in migraine sufferers with aura to cortical spreading depression (CSD). There is considerable evidence that cortical spreading depression (a better although less historical term would be cortical activation followed by neuronal depression) underlies the migraine aura[2,3]. In support of this, when one of the genetic mutations in the CACNA1A gene on chromosome 19 which underlies some cases of hemiplegic migraine was inserted into "knock in" mice, this led to a lowered threshold for the initiation of cortical spreading depression[4]. The obvious conclusion would be that the cerebral cortex of migraine sufferers is in some ways hyper excitable. However, cortical responsiveness is a complex issue, and for example it has been concluded that the sensory cortices of migraineurs react excessively to repetitive, but not to single stimuli[5].

The recent identification of a specific gene mutation which underlies migraine with typical aura in a large Canadian family once again implicates changes in neuronal excitability[6]. This gene, the KCNK18 gene which codes for the TRESK K2 potassium channel causes a frame shift which prematurely truncates a potassium channel protein, thereby likely changing neuronal excitability.

The neuronal changes in migraine go far beyond the cerebral cortex. These changes have taken much longer to identify than those in some other neurological diseases, likely due in part to a less concerted research effort, and perhaps also because they are more complex. However, the symptoms of migraine are gradually becoming understood. For example, there are projections from the retina which synapse on the third order sensory neurons in the thalamus that carry pain information from the dura to the cerebral cortex[7]. Therefore, when these thalamic neurones are sensitized during a migraine attack and are carrying pain information to the cortex, nerve impulses from the retina in response to bright light will facilitate this transmission of pain. The headache will therefore be exacerbated. Photophobia in the case of migraine is not really light sensitivity, but an exacerbation of the headache pain upon exposure to light. This convergence of retinal inputs on pain transmission pathways through the thalamus may be unique to pain pathways from the dura, and may explain therefore why photophobia is such a prominent feature of headache not just in the case of migraine but also in patients with meningitis.

Central to the generation of migraine pain is the concept of central sensitization. Peripheral sensitization of nociceptive nerve endings in the dura is thought to occur when activation of these results in the release of various molecules at nerve endings which increase their excitability. Central sensitization, that is, increased excitability of neurons in the central nervous system (CNS) pain pathways, can then follow, generated by prolonged nociceptive inputs from the periphery. This central sensitization can occur at several levels, including the nucleus trigeminal caudalis, and in the thalamus. Central sensitization can lead to allodynia, the perception of stimuli which are usually not painful as painful. Central sensitization at the thalamic level is particularly interesting, in that it can theoretically lead to allodynia in extra-cephalic sites. Extracephalic allodynia has been demonstrated to occur in migraine[8-10].

Another central concept in migraine pathophysiology is that there may be defective descending pain modulation from brainstem centers on inputs from the trigeminal nerve. A number of brainstem and hypothalamic structures appear capable of modulation of transmission through the trigeminal nucleus caudalis, including the posterior hypothalamus[1,11-14], the nucleus raphe magnus, the periaqueductal grey, and the nucleus cuneiformis. Possible dysfunction of one or more of these brainstem pain modulatory systems may result in excessive neural trafficking through trigeminal pain pathways, and this in turn may leads to the sensitization of these pain pathways so that they become "hyper excitable".

Kuan-Lin Lai and co-authors in this issue of the Canadian Journal of Neurological Sciences add one more piece to the emerging evidence for changes in CNS function in migraine sufferers[15]. By using an evoked response paradigm, the found evidence for hyper excitability in thalamocortical projections in patients with migraine. This hyper excitability was present both ictally during the migraine attack, and also intericatlly when the patient was pain-free. Their findings of an abnormality interically is consistent with the notion that pain transmission pathways in the migraine sufferer are not normal, and that the abnormal pain transmission that results may then lead to further abnormalities due to the development of central sensitization. Their findings are not without controversy, however, and the literature to date on the results of evoked response testing in migraine is conflicting. This is perhaps not surprising, given the complexity of the CNS and also the technical complexity of this investigative method. However, other methods of interrogating the CNS pain pathways have also indicated hyper excitability in

thalamocortical projections. Based on fMRI data, Burstein et al[9] concluded that the thalamic pain relay neurons respond much more strongly to innocuous stimuli during a migraine attack than they do between attacks, indication central sensitization of these neurons during the migraine headache. Neuronal recordings in rodents has also confirmed that when the dura is irritated, thalamic neurons respond much more vigorously to stimuli applied elsewhere on the body[9].

Clearly confirmatory studies are needed before the results of the study by Kuan-Lin Lai can be fully accepted, given the conflicting data in the medical literature. However, a picture of migraine pathophysiology seems to be slowly emerging, although this pathophysiology may differ somewhat from patient to patient, depending on the genetic underpinning of their migraine disorder. At least in migraine with aura, an increased propensity to CSD related to changes in cortical excitability may initiate the attack. The diffusion of substances released during the initial intense neuronal activation phase of CSD to nearby vascular nociceptors may be responsible for their activation and the initiation of the pain phase of the migraine attack[16]. In migraine without aura, it may be that a somewhat similar phenomenon occurs[17]. The painful inputs into the trigeminal system may then not be handled normally due to defective pain modulation mechanisms in the brainstem. Increasing central sensitization of pain pathways to the cortex may then occur, either because the relay neurons themselves are hyper excitable or because of defective brainstem pain modulation. This central sensitization may initially be present only during the migraine attack, but may in some patients become more persistent as the patient's migraine progresses to the chronic daily headache of chronic migraine.

Which of the details in the above hypotheses are correct, and in which patients still needs to be worked out. However, one thing is certain. We need to listen to our patients, and would do well to try to better understand their symptoms through further research. The recent work of Noseda et al[7] has given us a basis upon which to understand photophobia. Of interest, they also mapped the axonal projections of dura-sensitive thalamic neurons to the cerebral cortex. The cortical terminal fields of these trigeminal pathways were indeed large. In addition to dense projections to the thalamic reticular nucleus, these axons branched widely in multiple cortical regions including the primary somatosensory cortex, the primary and secondary motor cortices, primary and secondary visual cortices, and the parietal association cortex, among others. Axonal branches went through cortical layers I through V. When our patients complain of non-specific symptoms like cognitive change, incoordination, and visual blurring it may be that these intense inputs from an abnormally sensitized thalamus are playing havoc with cortical function in some of these areas. Migraine is indeed more than just a headache.

No doubt more research over the next few years will bring us ever greater insights into this very complex neurobiological disorder. Neurologists are fortunate to have a ring-side seat as this drama unfolds.

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