Magnesium and glutamate

The magnesium ($\text{Mg}^{2+}$) ion is essential for effective cellular energy metabolism and also for the stability of cell membranes. In the neuron $\text{Mg}^{2+}$ regulates in part the influx of ionized calcium through NMDA channels. Low brain $\text{Mg}^{2+}$ has been implicated as a potential factor in neuronal hyperexcitability that is associated with a susceptibility to spreading depression. In this issue of Cephalalgia, Gallai and co-workers report lowered red blood cell $\text{Mg}^{2+}$ levels in migraine patients. I find the results interesting because they confirm by peripheral measures the low brain $\text{Mg}^{2+}$ levels reported by Ramadan and his colleagues using 31-PMR spectroscopy. In this study, the reduction of $\text{Mg}^{2+}$ was significant only during migraine attacks, while Gallai et al. found reduced levels both during and between attacks. This study is also of value because of the large number of patients studied. The results fit well with an accumulating literature that suggests low levels of $\text{Mg}^{2+}$ in blood, serum and saliva in migraine patients. Some caution must be exerted in interpreting these data, however, because red blood cell $\text{Mg}^{2+}$ is an unsatisfactory index of intracellular or total body $\text{Mg}^{2+}$ in circulating blood. Measurement of $\text{Mg}^{2+}$ levels in blood monocytes or ionized $\text{Mg}^{2+}$ is preferable.

Also in this issue of Cephalalgia, Martinez and co-workers report elevated glutamate levels in CSF of migraine patients studied during the attack; the elevation was found to be more pronounced in migraine with aura. These results are of importance because glutamate measured in CSF provides a more direct indication of disordered brain glutamate turnover in connection with the migraine attack than has been previously established. We and others have found elevated glutamate levels in platelets used as a peripheral model for neurons. The relation between plasma glutamate levels to those in the CNS remains uncertain. The reports by Ferrari described significantly increased plasma glutamate levels in migraine with aura. In contrast, plasma glutamate levels in the present study by Martinez and co-workers are significantly lower than "stressed" controls. The contradictory results may be due partly to different control groups.

Whatever, the results of the Gallai and Martinez studies are in keeping with the concept of migraine as a state of central neuronal hyperexcitability and spreading depression as the mechanism of migraine. Low brain magnesium increases the susceptibility to spreading depression and glutamate elicits and supports spreading depression. If these results are confirmed by other laboratories, this emerging concept of the cause of migraine will be strengthened.

GIOVANNI D'ANDREA

Blood flow in the CCA

In their article in this issue, Drs Hannnerz and Jogestrand continue to expand the beachhead in the relationship between the inflammatory changes described in cluster headache and the changes in vascular reactivity.

Their study was on the effect of common carotid artery (CCA) blood flow of nitroglycerine in 18 patients with cluster headache and 5 controls. Not surprisingly, nitroglycerine produced an increase in flow in the common carotid artery in the controls. The increase was less in the patients with active cluster headache. This finding is in keeping with the changes noted in the middle cerebral artery (MCA) of patients with active cluster after inhalation of CO$_2$. Both suggest that these vessels are already dilated and have little capacity to dilate further. In the inactive phase the responses of both the common carotid artery and the middle cerebral artery of cluster patients reverts to the response found in controls. Patients who were studied in spontaneous cluster attacks were noted to have a bilateral increase in vascular resistance as the pain became maximal. This is compatible with the idea that the reflex constriction of arteries distal to the common carotid artery was not affected in spontaneous cluster, although it was blocked by nitroglycerine.

It is unclear whether the increase in vascular resistance occurs at the time the pain is reaching a crescendo and acting as a damper on the process, or whether it is part of the pain provoking stimulus. The fact that hyperventilation produces a temporary amelioration of the pain suggests the former. Thus the authors propose a mechanism whereby the capacity of the venous drainage of the cavernous sinus, reduced by the putative inflammation which invests it periodically, is assaulted in conditions which produce increased venous return, only to be rescued by a reflex arterial vasoconstriction. This vasoconstriction persists and leads to the refractory time usually found after each cluster attack.

This paper adds yet more pieces to the puzzle surrounding the mechanism of this most fascinating and vexing condition.

MJ GAWEL

Intranasal capsaicin administration

The article by Marks et al. in this issue on intranasal capsaicin administration represents a new and interesting approach to the therapy of cluster headache. The results of the study agree with those obtained in previous reports which have not been mentioned (1, 2). It contains, however, some incongruities. Non-parametric statistical tests would be more appropriate to evaluate the data. Despite the high male prevalence of cluster headache, the study population was composed of 10 females and 3 males. This uneven
distribution is unlikely to be ascribed, as stated by the authors, to the small size of the patient population. In addition, one of the problems of evaluating the benefits of capsaicin is the difficulty of blinding its administration. Double-blind placebo-controlled trials cannot be performed readily with capsaicin. In this study camphor was not capable of simulating the same local effects evoked by capsaicin such as rhinorrhoea and burning. Local reactions to the intranasal treatments are not reported in the article. Despite these criticisms there is a beneficial effect when intranasal capsaicin is instilled on the same side of the cluster headache attack (2). The clear ineffectiveness when patients were treated in the contralateral nostril seems to indicate that a placebo mechanism cannot explain the capsaicin. Therefore the few studies carried out so far indicate that intranasal capsaicin could be used effectively in the therapy of cluster headache. We encourage the establishment of a capsaicin study group with the goal of clarifying the effectiveness of topical capsaicin in cluster headache.

REFERENCES


MARCELLO FANCIULLACCI