

## Editorial Commentary

### Sensitivity to light and noise

Neurophysiological experiments in laboratory animals and humans have convincingly demonstrated the development of "central sensitization" in response to repeated discharge of primary afferent nociceptors (1, 2). Convergence of low-threshold mechanoreceptive neurons on spinothalamic tract neurons that have been sensitized by nociceptive input is thought to account for tenderness around the site of injury. It now seems clear that abnormal persistence of this sensitization process contributes to sensory disturbances experienced by many patients with chronic pain syndromes (3). Low-grade nociceptive input appears to be sufficient to maintain symptoms of central sensitization in certain patients with chronic pain syndromes (4); in others, nociceptive input seems unnecessary (5), implying that central changes mediate sensory disturbances (6).

In many respects, the development of sensitivity to normally innocuous levels of light and noise during headache resembles the process of "central sensitization" demonstrated neurophysiologically in spinothalamic tract neurons. The persistence of visual and auditory sensitivity between episodes of headache may be analogous to the persistence of tenderness for hours or days after injury. In this issue of *Cephalalgia*, Vanagaite-Vingen and colleagues report on sensitivity to light and noise in patients with cluster headache, and on sensitivity to noise in migraine. Their reports confirm the clinical impression that photophobia persists between attacks during bouts of cluster headache, and also demonstrate that patients are unusually sensitive to noise when in a bout. Importantly, Vanagaite-Vingen et al. found that sensitivity to light and noise returned to normal between bouts of cluster headache. In contrast, patients with migraine reported that discomfort to low levels of noise persisted during the headache-free interval. The intensity of phonophobia between attacks of migraine was not related to usual headache frequency; however, the

association between phonophobia and time since the last attack was not investigated, leaving open the possibility that this symptom might eventually disappear in patients with infrequent attacks (7).

Vanagaite-Vingen's findings emphasize that sensory disturbances persist between attacks of migraine and cluster headache. Perhaps these disturbances are residual symptoms of "central sensitization" (analogous to tenderness after injury). Alternatively, they may be an indication of persistent low-grade activation of peripheral or central nociceptive mechanisms that contribute to headache (analogous to persistent sensory disturbances in certain chronic pain syndromes). If indeed there are parallels between sensitization of spinothalamic tract neurons and the mechanisms that contribute to photophobia and phonophobia, then treatments which reverse central sensitization (e.g., 8) might decrease susceptibility to headache; furthermore, sensitivity to light and noise may turn out to be useful markers of the effectiveness of preventative therapy.

#### REFERENCES

1. Simone DA, Sorkin LS, Oh U, Chung JM, Owens C, LaMotte RH, et al. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. *J Neurophysiol* 1991;66:228-46
2. Torebjörk HE, Lundberg LER, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol (Lond)* 1992;448:765-80
3. Koltzenburg M, Torebjörk HE, Wahren LK. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain* 1994;117:579-91
4. Rowbotham MC, Fields HL. The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. *Brain* 1996;119:347-54
5. Baron R, Maier C. Painful neuropathy: C-nociceptor activity may not be necessary to maintain central mechanisms accounting for dynamic mechanical allodynia. *Clin J Pain* 1995;11:63-9
6. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992;355:75-8
7. Woodhouse A, Drummond PD. Mechanisms of increased sensitivity to noise and light in migraine headache. *Cephalalgia* 1993;13:417-21
8. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994;59:165-74

PD DRUMMOND

### Deficient interictal habituation

Wei Wang and Jean Schoenen demonstrate that deficient interictal habituation, expressed by a potentiation of AEPs, occurs in migraine patients. This is a very important finding since, in previously published contingent negative variation (CNV) studies, the pronounced negativity in migraine patients could be explained by higher negative amplitudes, due to greater cortical arousal, and also by reduced habituation as a result of a long-lasting orienting reaction. The basic mechanism of increased CNV negativity is still unknown. The present publication supports the theory of habituation-linked changes of cortical potentials, which contradicts simplified aspects of higher cortical activity. This leads to an interesting combination of psychological and neurophysiological factors affecting habituation. From a neurophysiological point of view, an excessive lactate accumulation leads to metabolic changes. Low serotonin activity correlates with deficient habituation parameters. With regard to psychological aspects, habituation is the ability to say "no" and to learn not to react to all stimuli. Can habituation be trained using psychotherapy or be influenced by medication? What are the reasons for metabolic disequilibrium in migraine patients? When did this dishabituation start—at the moment of the first migraine attack or even earlier? What are the exact relations between behavior and neurotransmitter change? These questions will probably be answered in the next few years.

P KROPP

## Physical therapy: a role in migraine?

It is enigmatic that, in some circles, physical therapy is prescribed for migraine. Not only is there no evidence from controlled trials that it works, there is no substantive rationale for this practice. Perhaps it is based on the mistaken reasoning that, because patients with migraine exhibit tender neck muscles and impaired neck movement, physical therapy should help their pain. This reasoning collapses if it is recognized that muscle tenderness and contraction are secondary to the pain of migraine.

The paper by Marcus et al. in this issue should bring little cheer to proponents of physical therapy. Their study 1 shows conclusively that physical therapy is ineffective for migraine. In the face of such data the prescription of physical therapy for migraine should cease, wherever it remains a fashion.

Marcus et al. concede a possible, but selective, role for physical therapy in the management of migraine—for patients wanting non-pharmacological treatment who have failed relaxation and thermal biofeedback. The data in support of this concession, however, are less compelling than those of study 1. The authors acknowledge that study 2 was compromised by a selection bias; only patients volunteering for further treatment entered the study. Furthermore, the group sizes were small; consequently the confidence intervals of the proportions of patients who improved are large. The degree of improvement achieved in study 2 was less than that in study 1, and the success rates cannot be compared. Consequently, despite the generosity of the authors towards physical therapy, such solace as might be drawn from study 2 rests on a clinical effect that is mediocre at best.

N BOGDUK

## Sumatriptan nasal spray

"Stratification" of patients' migraine by analyzing time to peak intensity, associated disability (e.g., nausea), and overall severity often suggests the need for non-oral treatment. Nasal sprays can bypass the gastrointestinal tract.

The article by Ashford et al. in this issue is a post hoc meta-analysis of 2,395 patients in four studies on

sumatriptan nasal spray. It is an evaluation of the consistency of response across clinical subtypes. A concern about such an analysis (besides the obvious post hoc aspect) is the variability of placebo response. Fortunately for this evaluation, the relationship between active treatment and placebo did not vary much, with about 66% of patients treated with sumatriptan nasal spray and 33% of placebo-treated patients obtaining headache response at 2 h. This makes subsequent subgroup analysis more credible.

Sumatriptan nasal spray showed no significant clinical difference for gender, ethnicity, adult age, weight, or migraine type. Use of concomitant prophylactic medications also does not affect sumatriptan nasal spray effects, unlike rizatriptan, which requires a lower dose for patients on propranolol. Not surprisingly, no patient showed any "serotonin syndrome"-like symptoms when combining sumatriptan nasal spray with an SSRI.

Dahlöf et al.'s article presents prospectively gathered patient preference data; 57% preferred the nasal spray to tablet, 46% preferred nasal spray to injection, and 68% described bitter taste with the spray.

Dahlöf raises the critical issue of where the spray is absorbed and recommends alternative clinical instructions for minimizing bad taste and maximizing nasal mucosal absorption.

The two articles demonstrate efficacy and speed, suggesting a highly useful niche for the spray in bypassing the gut. It may be useful to provide patients with a "don't mantra" when instructing them in sumatriptan nasal spray use: "don't sniff, don't snort, don't inhale, don't swallow, don't tilt the head back, and don't lie down!"

SJ TEPPER

## NK-mediated links for migraine

Mosnaim and co-workers have performed an interesting study of lymphocyte trafficking in migraine, the results indicating an increase of normal T cells (CD3+) and overall of natural killer (NK) cell subsets (CD16+, CD56+) (Cephalalgia 1998;18:197-201). These cellular phenotypes were more in evidence interictally when compared to dur-

ing an attack and healthy subjects. What does this mean? Is it relevant for headache? How do these findings affect the most widely accepted hypotheses for migraine, such as "sterile inflammation" or the "nitric oxide" (NO) hypotheses?

The biologic message of this possibly sentinel study might stimulate speculation about the importance of the basic links between the NK cell population and vascular/endothelial inflammation mediators (i.e., NO) and a possible role in the molecular mechanisms of migraine (1, 2). The nitrinergic network in migraine remains to be determined (3), but the present results add to the solution. In fact, there is increasing evidence that NK cell activity is directly dependent upon the concentration of L-arginine, the main NO precursor (4). The basal NK subset increase in migraine may be the consequence of a similar increase of NO synthase activity determined by nitrite accumulation (5). The possible role played by the NK subset in migraine emerges from this report, although further functional investigation is needed to identify and define other factors which could influence the NK activity and the fine balance operating between neurotransmission and immunocompetence in migraine.

## REFERENCES

1. Renard V, Cambiaggi A, Vely F, Blery M, Olcese L, Olivero S, et al. Transduction of cytotoxic signals in natural killer cells: a general model of fine tuning between activatory and inhibitory pathways in lymphocytes. *Immunol Rev* 1997;155:205-21
2. Martelletti P, Stirparo G, Morrone S, Rinaldi C, Giacobozzo M. Inhibition of intercellular adhesion molecule-1 (ICAM-1), soluble ICAM-1 and interleukin-4 by nitric oxide expression in migraine patients. *J Mol Med* 1997;75:448-53
3. Olesen J, Thomsen LL, Iversen H. Nitric oxide is a key molecule in migraine and other vascular headaches. *Trends Pharmacol Sci* 1994; 15:149-53
4. Cifone MG, Cironi L, Meccia A, Roncaioli P, Festuccia C, De Nuntiis G, et al. Role of nitric oxide in cell-mediated tumor cytotoxicity. *Adv Neuroimmunol* 1995;5:443-61
5. Martelletti P, D'Ald C, Stirparo G, Rinaldi C, Giacobozzo M. Modulation of nitric oxide synthase by nitric oxide donor compounds in migraine. *Int J Clin Lab Res* 1998;128

P MARTELLETTI