Conceptual divide between adaptive and pathogenetic phenomena in migraine: nausea and vomiting

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Drummond and Granston (2004) believe that nausea and headache, two key symptoms of migraine, interact pathogenetically by reinforcing each other in a vicious circle during attacks. These authors elaborate upon the role of extracranial vasodilatation during optokinetic stimulation—painful as well as painless—in patients with migraine and control subjects, respectively, as an important component of the defence (flight-or-fight) response. In considering the pathogenetic role in migraine of extracranial neurovascular responses to stress, it bears emphasis that extracranial vasoconstriction—as seen in conjunctival vessels—is as frequently observed in migraine patients, as is vasodilatation (Blau and Davis, 1970). Skin pallor is commonly noted during migraine attacks (Lance and Anthony, 1971; Campbell, 1990). Elevations of plasma vasopressin sufficient to cause facial pallor have been seen in migraine attacks (Hampton et al., 1991) and the theoretical basis for an adaptive/defensive role for vasopressin elevations in migraine with pallor as one physiological trade-off has been discussed (Gupta, 1993, 1997). Extracranial neurovascular responses to stress are terminal events of the migraine cascade, which process can be initiated several hours or a few days before onset of the aura or the headache (Peatfield, 1988). In contrast to experimental nitroglycerine-induced migraine, alterations of extracranial blood flow are quite unlikely to exert a primary or major influence on the pathogenesis of spontaneous migraine attacks.

The hypothesis that normal inhibitory modulation of pain is disrupted in migraine patients during motion sickness (Drummond and Granston, 2004) has several critical limitations. It is important to consider, in the first instance, as with other theories of migraine (Blau, 1993), why antinociception should be spontaneously altered during remissions and exacerbations of migraine; equally important, there is no clinical evidence of impaired nociception in migraine (Gupta, 2003). The acute phase of migraine attacks (with or without aura) is associated with substantial increases in plasma methionine-enkephalin (analgesia-mediating opiate peptide) that return to baseline only slowly in the pain-free period (Mosnaim et al., 1989). Also, peripheral pain threshold to low-intensity stimulation was greater or unchanged during headache than during the headache-free interval, and the pressure–pain threshold was not correlated to the tenderness scores obtained by manual palpation, thereby eliminating the possibility of both a general ictal increase in sensitivity to pain and focal dysfunction in the antinociceptive system (Drummond, 1987; Jensen et al., 1988). Activation of the vasopressin-related adaptive ‘system’ also enhances antinociception during migraine attacks, the process beginning in the pre-prodromal and prodromal phases (Gupta, 1997, 2003). Despite noting that tolerance of discomfort does not generally differ between migraine patients and controls and suggesting that a learning process could underlie the ability of migraine patients to tolerate heightened levels of attack-related discomfort, Drummond and Granston (2004) maintain the validity of the dysfunctional pain modulation hypothesis of migraine pathogenesis in their analysis.

All documented phenomenological—clinical or laboratory—perturbations of migraine, including nausea and vomiting, have been consigned to presumed pathogenetic algorithms. Unless patients are viewed as being balanced between opposing forces pushing them towards health or disease—headache or headache-free state, the biology of migraine will remain at its infancy (Gupta, 1999, 2004). Use of the term ‘stress’ or the ‘flight-or-fight’ or ‘defence’ response in migraine pathophysiology carries little or no utility other than serving as a euphemism for ignorance, relegating as it does the significance of both post-stress aura and headache as well as the typical lateralization (unilateral, bilateral or side-shift) of headache (Gupta,
2004b). The analysis of the mechanistic bases of the many clinical modulators of migraine can be advanced in the framework of a recently elucidated biologically adaptive or protective ‘system’ (Gupta, 1997).

The focus on the simultaneous build-up and subsidence of nausea and headache (Drummond and Granston, 2004) should not be assumed to indicate that nausea and/or vomiting contribute to the pathogenesis of migraine or to dissociate theoretically the physiological significances to migraine pathogenesis of nausea or vomiting (Gupta, 2004c). Emesis clearly has an anti-diuretic action, indicating increased arginine-vasopressin (AVP) release (Rowe et al., 1979). Nausea itself, even without vomiting, is accompanied by intense and rapid AVP release (Faull et al., 1991). Mild nausea can distort physiological AVP responses because nausea is a more potent and predominating stimulus to AVP release (Rowe et al., 1979; Faull et al., 1991). Nausea-mediated AVP release predominates over concomitant inhibition by water loading (osmolar) or ethanol (pharmacological); the specificity of nausea-mediated AVP release is indicated by the absence of significant increases in plasma AVP, in contrast to human subjects, in rats (which lack an emetic reflex) given relatively large doses of apomorphine (Faull et al., 1991). As part of the adaptive system that can delay or abort migraine attacks, vasopressin promotes vasomotor control, antinociception and behaviour control (Gupta, 1997). Nausea and/or vomiting probably represent an important anticipatory or attack-related neuroendocrinological mechanism to limit the impact of headache in migraine patients (Gupta, 2004c).

References