"Migraine Pain Associated with Middle Cerebral Artery Dilatation: Reversal by Sumatriptan” (Lancet 1991;338:13–17), by L Friberg, J Olesen HK Iversen and B Sperling, merits attention because it describes the novel application of two non-invasive techniques to address the relationship between vessel dilatation and the pain of headache.

Ten migraineurs with unilateral headache were subjected to transcranial doppler sonography (to measure blood velocity within the middle cerebral artery) and single photon emission computerized tomography (to measure blood flow within the middle cerebral artery territory) in order to derive estimates of middle cerebral artery caliber changes in headache subjects. Both measurements were obtained shortly after headache onset and compared with measurements taken 30 min after administering sumatriptan. Sumatriptan abolished or significantly reduced the unilateral headache and increased middle cerebral artery velocity ipsilaterally, whereas blood flow remained unchanged. Based on a known mathematical relationship between vessel diameter and velocity when flow remains constant, the authors estimated that the middle cerebral artery diameter was increased by 20% on the headache side during the attack. The authors concluded that “headache pain was due to, or at least closely associated with, intracranial large artery dilation”, that “migraine headache originates from the dilated large arteries” and that “sumatriptan...predominantly acts on pathologically distended arteries”.

The combined use of transcranial Doppler and xenon blood flow measurements was reported initially by Dahl and colleagues in cluster headache patients (1). In their studies, headache and vasodilatation were not tightly coupled. Bilateral, not unilateral, increases in middle cerebral artery diameter were observed during spontaneous attacks. Moreover, decreases and not increases in vessel diameter were measured at the onset of pain when nitroglycerin was used to induce painful attacks. Discounting the important possibilities that (i) the middle cerebral artery may not be the source of headache pain in cluster or migraine, (ii) the middle cerebral artery may not be representative of the responses of other large pial vessels, and (iii) the headaches of cluster and migraine are different (albeit, they both respond to treatment with 5-HT<sub>1D</sub> agonists), the data from the Dahl study suggest that the relation between vasodilatation and headache cannot be defined simply by observing changes in vessel caliber.

Many investigators, including Harold Wolff (2) have written about the association between dilatation and the pain of headache. As noted above, some have suggested that dilatation and pain are causally related (3, 4), and certainly this is true during angioplasty. However, dilatation need not be the cause of pain in this condition and a correlation does not by itself establish a cause-and-effect relationship. Dilatation can develop as a consequence of perivascular pain fiber stimulation (3). Sensory fibers projecting to meningeal arteries, veins and sinuses from the ipsilateral trigeminal ganglion (see (5, 6) for review) contain potent vasodilating neuropeptides such as calcitonin gene-related peptide, neurokinin A and substance P. With depolarization, these neuropeptides can be released into the vessel wall by calcium-dependent mechanisms (7). As a consequence, vessels dilate and flow may increase. In support of this formulation, plasma levels of released neuropeptides (e.g. CGRP) increase within the internal jugular vein or sagittal sinus both during trigeminal stimulation in experimental animals (8) and man (9), and in humans with migraine headaches (10). Presumably, neuropeptide levels would have been elevated in Friberg’s patients with distended middle cerebral arteries. Hence, one possible interpretation of their data is that vasodilatation is not the cause of pain, but develops as a consequence of sensory neurogenic activation. The exact cause of this activation remains unknown, although algogenic substances from brain, blood vessel wall or vessel lumen have been implicated (11).

How, then, might sumatriptan alleviate the pain of migraine headaches? From the Friberg study, there is little doubt that vessel narrowing follows sumatriptan administration. However, it is unclear why sumatriptan did not narrow the contralateral middle cerebral artery or did not constrict the ipsilateral middle cerebral artery below its baseline diameter. Vasodilatation itself is not a prerequisite for sumatriptan-induced vasoconstriction (12, 13). Might inhibition of neuropeptide release and blockade of peptide-mediated vasodilatation underlie the drug-induced vessel narrowing? Recently, we observed two neuronally mediated actions of sumatriptan and...
related drugs which might explain the changes in vessel caliber and analgesia (8, 14–16). We reported that sumatriptan and the ergot alkaloids (i.e. 5-HT\textsubscript{1D} receptor agonists) attenuate the release of vasodilating neuropeptides from trigeminovascular fibers, probably by binding to receptors on perivascular fibers (prejunctional receptors) (8). Consistent with this finding, sumatriptan decreases plasma levels of CGRP in migraineurs (17) and inhibits the development of a neuropeptide-mediated sterile inflammatory response that manifests within the meninges following trigeminal stimulation (18–21). The inflammatory response is characterized by vasodilatation, endothelial and platelet activation as well as mast cell degranulation. In this formulation, the neurogenic inflammatory response contributes to the sensitization of vessels and to the prolongation of headache pain. A second important and related action of sumatriptan and ergot alkaloids is to block neural transmission within trigeminovascular neurons (16). These drugs blocked the expression of cellular activation within neurons of the trigeminal nucleus caudalis (laminae I, II\textsubscript{0}) following noxious stimulation of the meninges caused by injecting blood into the subarachnoid space. In this instance, the presence of the c-fos protein was used as a marker of cellular activation, and the trigeminal nucleus caudalis (laminae I, II\textsubscript{0}) as an important relay nucleus for nociception. Of interest, morphine blocks c-fos expression within this nucleus following the delivery of a nociceptive stimulus (i.e. formalin injection into the rat hindpaw) (21). Because blood in the subarachnoid space causes severe headache and is associated with intense vasoconstriction, the data suggest that constriction of dilated vessels is not the relevant prerequisite for 5-HT\textsubscript{1} induced analgesia in vascular headaches. In fact, recent data suggest that the 5-HT\textsubscript{1} receptor subtype mediating contraction of vascular smooth muscle may not be identical to the receptor which blocks neural transmission within trigeminovascular neurons (15). If true, it may be possible in the future to dissociate the two effects and to develop drugs which possess the analgesic effects only.

Based on contemporary concepts of pain physiology and current information, it is difficult to decide whether there is a role for vasoconstriction in the abatement of headache pain. In fact, vasoconstriction of the basilar and middle cerebral artery as well as extracranial segments of the internal and external carotid arteries was not observed after sumatriptan administration in one recent report (22), although relief of pain was. Assuming that vasoconstriction is important, one untested speculation holds that vasoconstriction might alter the geometry of perivascular fibers and, by so doing, affect the pain threshold. Another suggests that vasoconstriction may change transmural pressure in such a way as to reduce impulse traffic from sensitized vessels (6, 8, 14, 15). While these ideas await experimental scrutiny, Friberg, Dahl and their colleagues have provided an important new clinical direction and new tools with which to address relevant clinical questions. Do subjects who experience pain relief with sumatriptan or DHE exhibit the same vessel caliber changes as non-responders? Do correlations exist between diameter and headache severity, and between vessel narrowing and headache relief? Is there a temporal correlation between vessel narrowing and pain relief? Definitive answers may necessitate the use of sensitive magnetic resonance imaging methods, or other techniques which do not require assumptions about homogeneity and stability of cerebral blood flow. Nevertheless, the combination of techniques as described by Dahl, Friberg and their colleagues represents an important opportunity and a beginning.

References


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