MIGRAINE IS NOT PRIMARILY A VASCULAR DISORDER

Jes Olesen
University of Copenhagen, Glostrup Hospital, Dept. of Neurology, Glostrup, Denmark

A neural and a vascular hypothesis of migraine have been fighting for more than a century. The vascular hypothesis gained support in the mid-20th-century because it was shown that ergotamine was vasoconstrictor and those agents inducing migraine-like attacks such as histamine and nitroglycerine was vasodilators. The superstar of headache for several decades Harold G Wolff was a keen proponent of the vascular hypothesis and performed a long series of ingenious experiments. But unfortunately, with inadequate techniques available at the time. Thus, the vascular hypothesis became common knowledge and was the hypothesis presented in almost all text books. In 1981 we published the first of a series of studies of regional cerebral blood flow (rCBF) during migraine attacks. These studies were a blow to the vascular hypothesis in its simple form, because it was shown that there are no changes in brain blood flow during migraine attacks without aura, not even a hyperemic phase. Furthermore, although initial studies showed reduced perfusion in migraine with aura, the application of more sophisticated techniques demonstrated that these changes were spreading gradually across the cerebral cortex not respecting the territories of supply of major cerebral arteries. We proposed that these changes in cerebral blood flow are caused by a cortical spreading depression (CSD). Thus, the simple edition of the vascular hypothesis was mortified, but is there any role of blood vessels in migraine? We thought so and proposed that vascular changes are located in the cerebral and extra cerebral arteries and not in the tissue. Dilatation of arteries does not necessarily translate into changes in tissue blood flow and would hence be compatible with our findings. We demonstrated a slight dilatation on the pain side of migraine of the middle cerebral artery and the superficial temporal artery and proposed that this was not the direct cause of the migraine pain but was a reflection of the liberation of vasoactive substances from perivascular nerves. A simultaneous sensitization of nociceptors would be necessary to explain the pain. Furthermore, in a long series of provocation experiments we demonstrated that all agents able to induce a migraine attack are vasodilators. But there was one crucial exception, sildenafil. This PDE5 inhibitor can dilate blood vessels in certain areas of the body most notably the penis in erectile dysfunction. We found, however, no change in brain blood flow and no change in the diameter of cerebral and extra cerebral arteries after sildenafil. Calcitonin gene related peptide (CGRP) can induce migraine and is a strong vasodilator but the CGRP receptor antagonist telcagepant did not change brain blood flow or vascular diameters. Nevertheless, it was highly effective in the treatment of acute migraine attacks. It has long been debated whether the effect of triptans in migraine was due to their vasoconstrictor ability or to a neural mechanism. Triptans are effective on the 5-HT1b receptor which is vasocontrictive, but they are also effective on the 5-HT1d receptor and the 5-HT1f receptor, which are both located preterminally on nerve endings and do not constrict blood vessels. Very recently, the compound lasmiditan, which is a highly selective 5-HT1f receptor agonist, has proven effective in phase-II clinical trials by intravenous injection and as a tablet. It is thus proven beyond doubt that drugs with no vasoconstrictor action at all can be effective in the treatment of acute migraine attacks.

My conclusion is that vasoconstriction is not essential for the treatment of attacks and vasodilatation is not a major cause of migraine pain. The relative importance of the perivascular sensitization of nociceptors and of central enhancement of gain in the pain perception system has not been resolved. In all likelihood they of equal importance and occur simultaneously. Any small vasodilatation is at most contributory to migraine pain.