In this issue of the Journal of Neurophysiology Brennan et al. (p. 4143–4151) present a provocative, carefully conducted series of studies that challenge a very tightly held belief about cortical spreading depression (CSD) showing propagation of the dilation of cortical surface arterioles at a greater velocity than the wave changes in cellular activity. How could this be? Do not changes in blood flow follow neuronal changes passively with flow-metabolism coupling? It seems the issue is not that simple.

Cortical spreading depression (CSD) was first described by Leao (1944a,b), who observed a depression of electroencephalographic (EEG) activity that moved across the cortex at a rate of 3–6 mm/min. It has been observed in clinical practice that the migraine aura, a transient neurological disturbance (Headache Classification Committee of The International Headache Society 2004) that moves slowly across the visual field or over the limbs, has the same rate of progression at least for visual changes (Lashley 1941). The observation by Olesen and colleagues (1981) of a spreading reduction in cerebral blood flow, spreading oligemia, in patients with migraine aura triggered a revolution in thinking about migraine aura. For much of the 20th century, aura was considered a vascular process, i.e., primarily vasoconstriction as the initial event, with head pain as a consequence of a reactive vasodilation (Wolff 1948). The CSD hypothesis completely reversed this concept with the primary event being neural and brain blood flow changes being secondary to changes in neuronal activity (Lauritzen 1994). Indeed cerebral blood flow changes seen with single photon emission computerized tomography (Olesen et al. 1990) and perfusion-weighted magnetic resonance imaging (MRI) (Cutrer et al. 1998) lent support to this notion as a spreading oligemia was observed during aura, considered to be due to changes in neuronal activity, with different imaging modalities. Most recently functional MRI (fMRI) changes again consistent with CSD have been seen in migraine aura (Hadjikhani et al. 2001), so it is generally accepted that CSD is the animal experimental equivalent of migraine aura—thus its importance to human neurobiology.

It has been shown with single modality blood flow, such as autoradiographic methods (Duckrow 1941, 1944) or laser Doppler flowmetry (Piper et al. 1991), that triggering CSD results in a wave of reduced cortical blood flow. Moreover, using dual modality methods, such as laser Doppler flowmetry and extracellular electrophysiology (Akerman and Goadsby 2005; Goadsby et al. 1992), changes in neuronal firing and cerebral blood flow could be seen to occur together. However, these methods have lacked the combination of parallel spatial and temporal resolution. Brennan and colleagues (2007) have overcome this by combining electrophysiological measurements with optic intrinsic signal imaging. They show vasomotor changes in cortex traveling at significantly greater velocity than the neuronal changes, a circuitous pathway and crucially dissociation of vasomotor and neuronal changes. Their data suggest a mechanism that requires the vasculature and not the neuronal component. These data demand a complete re-evaluation of flow-metabolism coupling, blood flow changes that accompanying changes in demand for energy substrates in the brain (Edvinsson and Krause 2002), as the single explanation for brain blood flow changes in migraine. Moreover, the authors challenge the cerebrovascular physiology community to consider this remarkable new mechanism. As is typical for more interesting studies, the work by Brennan and colleagues raises more questions than it answers.

REFERENCES