

**Migraine, Epilepsy, and Migralepsy:  
Myths and Realities**

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Writing about migraine more than 100 years ago, in *The Borderland of Epilepsy*, Sir William R. Gowers noted: “. . .the two maladies are sometimes mistaken, and more often their distinction is difficult.”<sup>1</sup> Gowers’ observation is understandable —migraine and epilepsy are comorbid episodic disorders with numerous similarities.<sup>2</sup> For instance, migraine and epilepsy are chronic, episodic disorders that feature prodromal symptoms and electrophysiological changes that can manifest as aura. Both disorders also tend to affect otherwise healthy individuals; may be triggered by stress (or letdown from stress), fatigue, diet, photic stimulation, hormonal fluctuations/menstruation, or consumption of alcohol; have a genetic component; and are first experienced in infancy, childhood, or adolescence. In addition, migraine attacks have been known to trigger epileptic seizures (ie, “migralepsy”), and headache resembling migraine is a common by-product of seizures. Commonalities in the underlying cellular and molecular mechanisms may also explain why some antiepileptic drugs, including valproate, topiramate, and gabapentin, are effective antimigraine agents.<sup>2</sup>

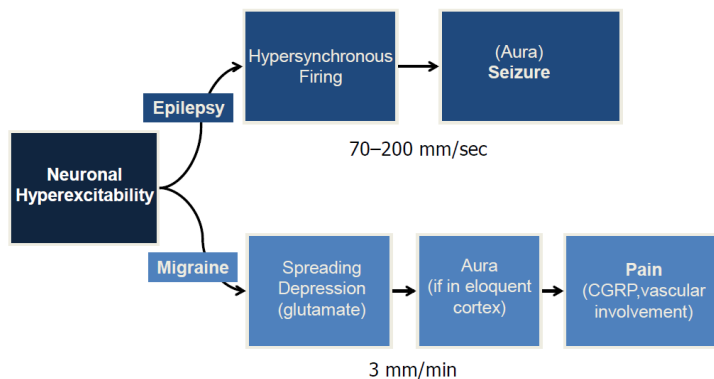
In the 1940s, a Brazilian doctoral student named Aristides A.P. Leão conducted experiments in which brief (1 to 5 seconds), repetitive electrical stimulation of the cortex or a few light touches with a small glass rod induced a "marked, enduring depression" of spontaneous electrical activity that spread out slowly in all directions from the stimulated region.<sup>3</sup> The phenomenon, which came to be known as cortical spreading depression (CSD), is now widely accepted as the basis for migraine aura and the trigger for headache pain. Research since then has shown that the phenomenon can also be induced by elevated extracellular potassium, glutamate, and inhibition of Na<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase (ATPase).<sup>2</sup> Grafstein's early studies on the ionic basis of CSD are particularly relevant to the issue of the commonality between migraine and epilepsy.<sup>4,5</sup>

A genetic basis for these similarities can be seen in mutations of the genes responsible for various forms of familial hemiplegic migraine and epilepsy. *CACNA1A* encodes the pore-forming subunit of neuronal P/Q type calcium channels<sup>6</sup> and is associated with episodic ataxia syndrome EA-2, the spinocerebellar ataxia syndrome SCA-6, and idiopathic generalized epilepsy.<sup>7</sup> *ATP1A2* encodes the  $\alpha$ 2 subunit of electrogenic Na<sup>+</sup>/K<sup>+</sup> ATPase<sup>8</sup> and has been linked with benign familial infantile convulsions,<sup>9</sup> alternating hemiplegia of childhood, basilar-type migraine, and migraine without aura.<sup>10</sup> *SCN1A* encodes the pore-forming  $\alpha$ 1 subunit of neuronal voltage-gated sodium channel

Na<sub>v</sub>1.1,<sup>11</sup> and has been implicated in generalized epilepsy with febrile seizures plus and severe myoclonic epilepsy of infancy.<sup>2</sup>

Migraine attacks, like epileptic seizures, may be triggered by excessive neocortical cellular excitability. In migraine, however, the hyperexcitability is believed to transition to cortical spreading depression rather than to the hypersynchronous activity that characterizes seizures.<sup>2</sup>

### Commonality of Epilepsy and Migraine



Ionotropic glutamate receptors play roles in both migraine and epilepsy—with NMDA receptors critical to cortical spreading depression of particular importance in migraine—and emerging candidates for drug therapy include NMDA, GluK1, and GluR5 antagonists. Systemic memantine inhibits the frequency and amplitude of spreading depression events induced by potassium chloride in the rat parietal cortex,<sup>12</sup> and there have been reports that memantine is effective in migraine prophylaxis.<sup>13</sup> Moreover, since R2B subunits are largely restricted to the forebrain, and the CSD implicated in triggering migraine attacks is a forebrain phenomenon, R2B selectivity may be useful for an NMDA antagonist. GluR5 antagonists are active in migraine models,<sup>14</sup> and intravenous LY293558, an antagonist of AMPA and GluR5 kainate receptors, dramatically improved headache in a small controlled clinical trial in acute migraine.<sup>15</sup> Topiramate, a functional antagonist of GluR5 kainate receptors (and AMPA receptors),<sup>16</sup> is widely used in migraine prophylaxis.

Greater understanding of the shared mechanisms of epilepsy and migraine can provide a basis for the development of improved treatment approaches that may be applicable to both conditions.

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