**Vagus Nerve Stimulation Inhibits Cortical Spreading Depression**

Shih-Pin Chen, Ilknur Ay, Tao Qin, Yi Zheng, Homa Sadhegian, Fumiaki Oka, Bruce Simon, Katharina Eikermann-Haerter,* Cenk Ayata.*

*Co-senior and co-corresponding authors

Neurovascular Research Lab, Massachusetts General Hospital, Harvard Medical School

---

**Objectives**

- To investigate whether vagus nerve stimulation (VNS) improves migraine by reducing cortical spreading depression (CSD) susceptibility.

**Background**

- VNS has recently been reported to improve symptoms of migraine.
- CSD: an electrophysiological event underlying migraine aura, and a trigger for headache.
- CSD is a shared target of action for migraine prophylactic drugs.
- VNS activates nucleus tractus solitarius, locus ceruleus and dorsal raphe nuclei, all of which can suppress CSD susceptibility.

**Methods**

- **Study animals:** male adult Sprague Dawley rats (n=52)
- **VNS (on the right vagus nerve):** Paradigms of VNS as widely used in epilepsy, depression and stroke
  1. noninvasive VNS (nVNS)
     - stimulation vs. sham
     - ms pulse of 5kHz sine waves at 25 Hz
  2. invasive direct VNS (iVNS)
     - stimulation vs. sham vs. naïve
     - 0.5mA, 30s train of 0.5ms pulses at 20Hz
- **Assessment of SD susceptibility:**
  1. the electrical threshold to evoke SD
  2. SD frequency upon continuous topical KCl
- **Cerebral blood flow (CBF) with LDF**

**Results**

**Discussion**

- VNS elevates the electrical threshold for CSD induction and reduces the frequency of KCl-evoked CSDs.
- The mechanism may be attributed to modification of monoaminergic pathways, neurotransmitters (glutamate/GABA), and proinflammatory cytokines.

**Conclusions**

- Our findings provide a potential mechanism by which VNS may be efficacious in migraine, and suggest animal models of CSD as a suitable platform to optimize efficacy of VNS on migraine.

**Acknowledgement**

This work was funded in part by the American Heart Association (10SDG2610275, KEH; 10SDG2600218, IA), the Massachusetts General Hospital (Claffin Distinguished Award, KEH), and an unrestricted research gift from Electrocore LLC.