**Major Ischemia Transforms Cortical Spreading Depolarizations into a Pathophysiological Process Producing Neuronal Death**

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**Introduction**

Cortical spreading depolarization (CSD) is a massive electrical depolarization of neurons and astrocytes that propagates as a wave throughout the brain cortex. CSD disrupts cellular ionic gradients, produces edema, and depletes energy stores as ionic pumps try to restore homeostasis. This physiological phenomenon exists on a continuum from a benign process involved in the aural phase of a migraine to a pathologic mechanism of secondary brain injury expansion in the penumbra of severe traumatic brain injury patients. In healthy tissue, CSD is accompanied by a physiological neurovascular coupling (transient hyperperfusion) supplying the tissue with the necessary energy for cellular recovery. In injured tissue, neurovascular coupling is compromised with CSD resulting in a transient hypoperfusion (spreading ischemia). This further depletes energy stores, which leads to longer depolarizations and contributes to cell death.

**Hypothesis**

A threshold of ischemia transforms CSDs into a pathophysiological process producing neuronal death.

**Methods**

We developed a novel four-vessel occlusion procedure in rats with an inflatable cuff around the right common carotid artery allowing tight regulation of brain perfusion. While controlling total brain perfusion, CSDs were induced by application of 1M KCl to a frontal craniotomy with electrophysiological and regional cerebral blood flow recordings occurring at separate posterior craniotomy sites. Histology was performed to confirm neuronal degeneration.

**Results**

Using the novel four-vessel occlusion model, we were able to control perfusion to the brain. A 14 % reduction in cerebral blood flow did not significantly alter the duration of the CSD or the magnitude of the hemodynamic response. However, a 59% reduction in cerebral blood flow significantly increased the duration of CSDs by 180% (control 60.3±4.1:  ischemia 169.3±18.0 s) while also significantly transforming the hemodynamic response from a hyperperfusion (161.5 ±31.7% increase) to a hypoperfusion (-4.3 ±3.4% decrease).

**Conclusion**

Major ischemia (~60%) can transform CSDs into a pathophysiological process leading to neuronal death.

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