Cortical Spreading Depression (CSD) in a CCM (Cerebral Cavernous Malformation) Mouse Model

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Introduction

Inducible knockout (KO) of the 3 cerebral cavernous malformation (CCM) genes, Krit-1, CCM2 and Pdcd10 has been used to study the functional and structural endothelial cell aberrations associated with CCM and to help elucidate the molecular mechanisms involved in lesion formation in a murine model. Recent studies on middle cerebral artery vessels from Krit-1 and CCM2 KO mice demonstrated a deficiency in endothelial-dependent vasodilation that can be rescued with the superoxide scavenger, Tempol. To date there has been no in-vivo investigation into the neurovascular behavior in CCM knockout mice with cortical and subcortical vascular lesions. Our study evaluates neurovascular coupling in CCM mice using optical intrinsic signaling (OIS) to study cerebral blood volume responses to direct visual and sensory stimulation and to study cortical spreading depression (CSD) induced with increasing concentrations of KCl.

Methods

KO mice induced between postnatal days 1-7 as well as their non-induced control litter mates were subject to a controlled experimental design utilizing optical intrinsic signal imaging of the fronto-parieto-occipital cortex to evaluate for sensory responses to visual and hindpaw stimulation as well as KCl-induced CSD (see figure).

Results

Seventy percent (7/10) of KO mice had a second CSD versus 20% (2/10) of control mice. CSD in KO mice seems to be more often facilitated (10/10 vs 4/10) by sensory input and has a greater propagation velocity compared to control mice.

Learning Objectives

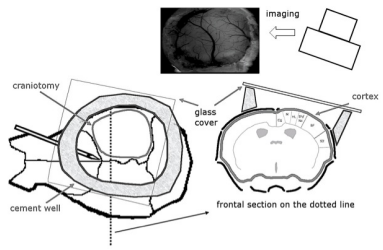
1. Understand the difference in CSD characteristics between KO and Control mice.
2. Understand the clinical and therapeutic implications behind the different CSD characteristics.
3. Understand the function and utility of OIS (optical intrinsic signaling) in detecting cerebral blood volume (CBV) changes and mapping functional regions of the brain.

References

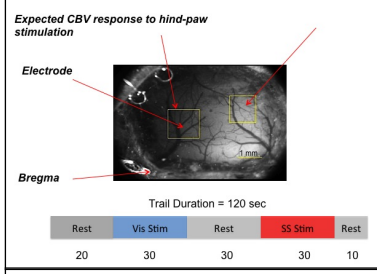
Conclusions

A mutation in any one of the 3 CCM genes leads to dysfunctional endothelial cells, which perturbs normal endothelial dependent vascular response. Cortical spreading depression, a well-conserved phenomenon involving neurovascular coupling appears to be different in CCM KO mice versus control mice. KO mice are more likely to have multiple CSDs that are more often facilitated by sensory input with a greater propagation velocity. This may have important clinical and therapeutic implications.

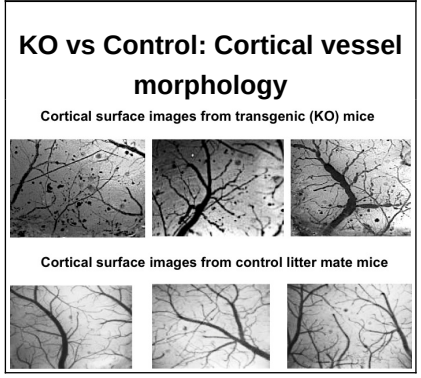
Experimental Preperation



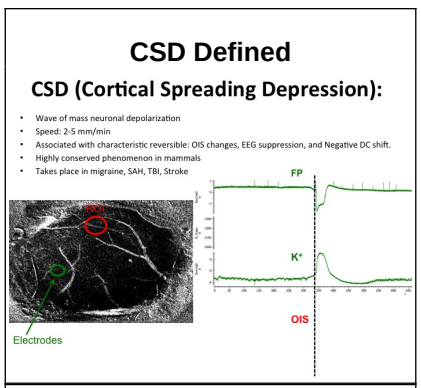
Cranial Window



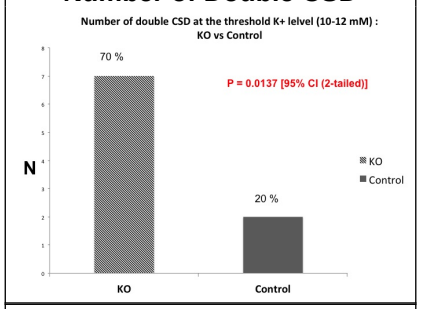
KO vs Control: Cortical vessel morphology



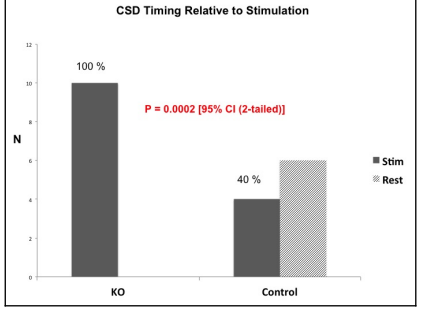
CSD Defined



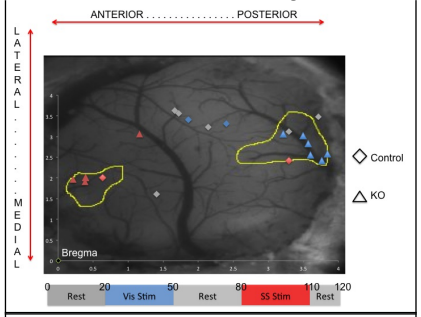
Number of Double CSD



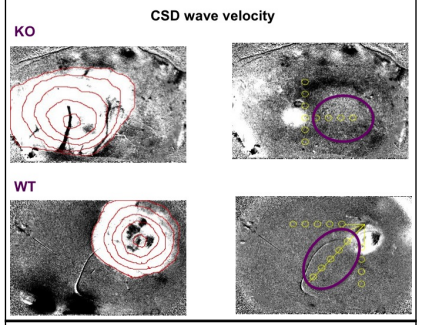
Onset of CSD timing relative to time of stimulation



CSD origin and timing relative to stimulated sensory cortex



CSD Velocity: KO vs Control



Mean change in CSD Velocity: KO vs Control