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Developing a Model for Slow Hypoxic Injury and Vascular Degeneration in Amyloid Burdened Brains.

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The breakdown of neurovascular systems may play a crucial role in the pathogenesis of Alzheimer's disease. However whether this breakdown initiates a degenerative mechanism or is the consequence of some other deleterious process remains unknown. We examined hippocampal pathology in double transgenic mice overexpressing a human mutant gene encoding the amyloid precursor protein (APPSwe/Ind) using a combination of histochemistry and stereologic techniques. Expression of APPSwe/Ind in these mice is driven by a tetracycline-sensitive promoter. Tetracycline transcriptional activator (tTA), the second transgene, is driven in turn by a CAM KIIa promoter that is only active in neurons. Thus this double transgenic construct allows us to control expression of APPSwe/Ind with doxycycline. Utilizing this characteristic, we created three distinct experimental groups: A, display abeta plaque pathology and express APPSwe/Ind at time of sacrifice; B, display abeta plaque pathology but do not express APPSwe/Ind at time of sacrifice; and C, do not display abeta plaque pathology but do express APPSwe/Ind at time of sacrifice. Stereologic investigation revealed decreased hippocampal volume in groups A(n=5) and B(n=5) when compared to group C(n=5) and age-matched wildtype (n=9) (p

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Real-time visualization of intracellular potassium dynamics in mouse macrophages during inflammasome-associated processes.

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Inflammasomes are caspase-1-activating, multiprotein platforms that mediate processing and secretion of pro-inflammatory cytokines and cell death in macrophages in response to host danger signals and pathogen invasion. It is well recognized that potassium efflux from the cell is a critical step for caspase-1 activation by inflammasomes in response to most stimuli. However, existing methods for directly investigating potassium in live cells are limited and most studies focus on bulk cell biochemical measurements or indirect indicators of pathway inhibition. Using novel intracellular potassium sensors and laser scanning confocal microscopy we demonstrate visualization of real-time potassium dynamics in live mouse macrophages. Specifically, we describe the kinetics of potassium efflux via the P_2X_7 purinergic receptor stimulated by exogenous ATP (active pathway) as well as the potassium ionophore nigericin (passive pathway). Further, we describe the mobilization of the mitochondrial potassium pool