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Presentation Abstract

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Presentation Title:	Improved methods for acute brain slice preparation from adult and aging animals (Part II): Glutathione depletion underlies rapid deterioration of adult brain slices
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Abstract:	The development of the living acute brain slice preparation nearly a half century ago was a pivotal achievement that greatly influenced the landscape of modern neuroscience. Acute brain slices are considered the gold-standard model system for detailed cellular, molecular, and circuitry level analysis and perturbation of brain function. A critical limitation of this model system is the extreme difficulty in preparing healthy slices suitable for visualized whole-cell patch clamp recordings from adult and aging animal. Thus, the vast majority of whole-cell patch clamp investigations have been carried out in acute brain slices derived from juvenile or adolescent animals. We previously reported that sodium ion replacement during the initial recovery step (but not during the slicing procedure) was necessary and sufficient for a dramatic improvement in neuronal preservation of acute brain slices from adult and aging animals. Thus, we have coined the term “NMDG protective recovery method,” a modified procedure that we found to perform superior in direct comparison with the most commonly employed “sucrose protective cutting method” in the context of adult brain slice preparation. We also recommended specific aCSF modifications and procedural changes to “access” diverse neuronal types throughout the brain and across the entire lifespan of the mouse. Here we extend these earlier findings to provide new mechanistic insights about why adult brain slices deteriorate rapidly after slicing. We present novel strategies to specifically combat these detrimental changes in order to stabilize slice health and drastically prolong slice longevity. Specifically, we find that neuronal glutathione content is severely compromised following brain slice preparation from adult animals. Glutathione depletion is a primary insult leading to the majority of the morphological and functional deterioration of neurons within adult brain slices over time, as this deterioration can be halted and even ameliorated to a large extent by replenishing intracellular glutathione levels or

facilitating de novo glutathione synthesis during the early stages of acute brain slice incubation. Thus, we demonstrate a powerful new approach combining our "protective recovery method" together with de novo glutathione synthesis as a simple and viable new strategy for preparing mature adult brain slices. These new principles will unlock the full potential of the acute brain slice preparation by enabling more detailed investigations of synaptic and circuitry function in normal aging and age-dependent neurological disorders that were previously considered extremely difficult or entirely not feasible.

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