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In vivo functional NADH imaging with single-cell resolution

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Abstract:

β-nicotinamide adenine dinucleotide (NADH) is the principal electron carrier in glycolysis, the Krebs cycle and the mitochondrial respiratory chain. NADH is generated during glycolysis and also produced from its oxidized form NAD^+ during mitochondrial oxidative metabolism that utilizes pyruvate derived from glucose. Subsequently, NADH is oxidized in the electron transport chain that establishes a potential across the inner mitochondrial membrane, enabling the production of ATP. Therefore, the ratio of NADH/NAD^+ depends on the balance of oxidative phosphorylation and non-oxidative glycolysis.

Since NADH molecule is fluorescent while NAD^+ is not, intrinsic NADH fluorescence serves as an indicator of the cellular redox state. Previous studies *in vivo* established that on a macroscopic level NADH auto-fluorescence of brain tissue *decreases* in response to sensory stimulation, cortical spreading depression or seizures throughout the duration of the stimulus as far as blood flow is not compromised, and *increases* in response to hypoxia or ischemia. A recent 2-photon microscopy study in hippocampal brain slices revealed that astrocytes have a higher resting NADH fluorescence than neurons and respond to stimulation of Schaffer collaterals with an increase in NADH signal [1].

However, cell specific NADH behavior *in vitro* might differ from *in vivo* because of the limited O_2 availability in the absence of blood flow and O_2 carriers. To test this, we performed *in vivo* 2-photon imaging in rat somatosensory cortex under resting conditions and in response to either sensory stimulation or hypoxia. Astrocytes were labeled with SR101 using topical loading. Our results indicate that we can easily resolve astrocytic cell bodies and their processes based on a higher resting level of NADH fluorescence in the cytosol, consistent with prior reports showing that almost all astrocytic NADH (>90%) is cytosolic. Astrocytic

NADH signal increased in response to transient (10 sec) hypoxia. Subsequent to the termination of the hypoxia NADH signal displayed a decrease and slow return to the baseline. NADH signal change was also observed in response to sensory stimulation. While preliminary, these results do suggest that *in vivo* imaging of NADH autofluorescence can provide a cellular-level biomarker for compromised oxygenation in models of neurodegenerative disease and stroke.

[1] Kasischke, K. A. et al., *Science* 305 (5680), 99 (2004).

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