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Evaluating the Utility of pPDH as a Marker for Neuronal Inhibition

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For many years, immediate early genes have been used to mark neuronal activation, and these markers have been instrumental in neuroscience research, specifically in the mapping of neuronal circuits that are activated by stimuli. However, no equivalent marker existed for the inhibition of neurons until 2024, when the phosphorylation of pyruvate dehydrogenase (pPDH) was identified as having an inverse correlation with action potential firing intensity. This study aims to determine if pPDH is a reliable tool for visualizing neuronal inhibition resulting from various drug-induced and internal states, specifically those mediated by GABAA agonists, Kappa Opioid Receptor (KOR) agonists, and hM4Di, an inhibitory Gi-DREADD. We found that isoflurane exposure, I.P. injection of ethanol, and I.P. injection of muscimol significantly increased expression of pPDH in the hypothalamus (Hyp) and the basolateral amygdala (BLA), while intraperitoneal (i.p.) injection of KOR agonist U50,488, chemogenetic inhibition of the nucleus accumbens through the DREADD hM4Di, and dynorphin release resulting from social defeat stress did not lead to a significant increase in pPDH expression. From these results, we conclude that pPDH is a useful marker for detecting inhibition mediated by GABAA receptor agonists, but not as useful for visualizing inhibition mediated by G-Protein coupled receptors or by internal states such as stress.