Characterization of A Novel Marker for Neuronal Inhibition

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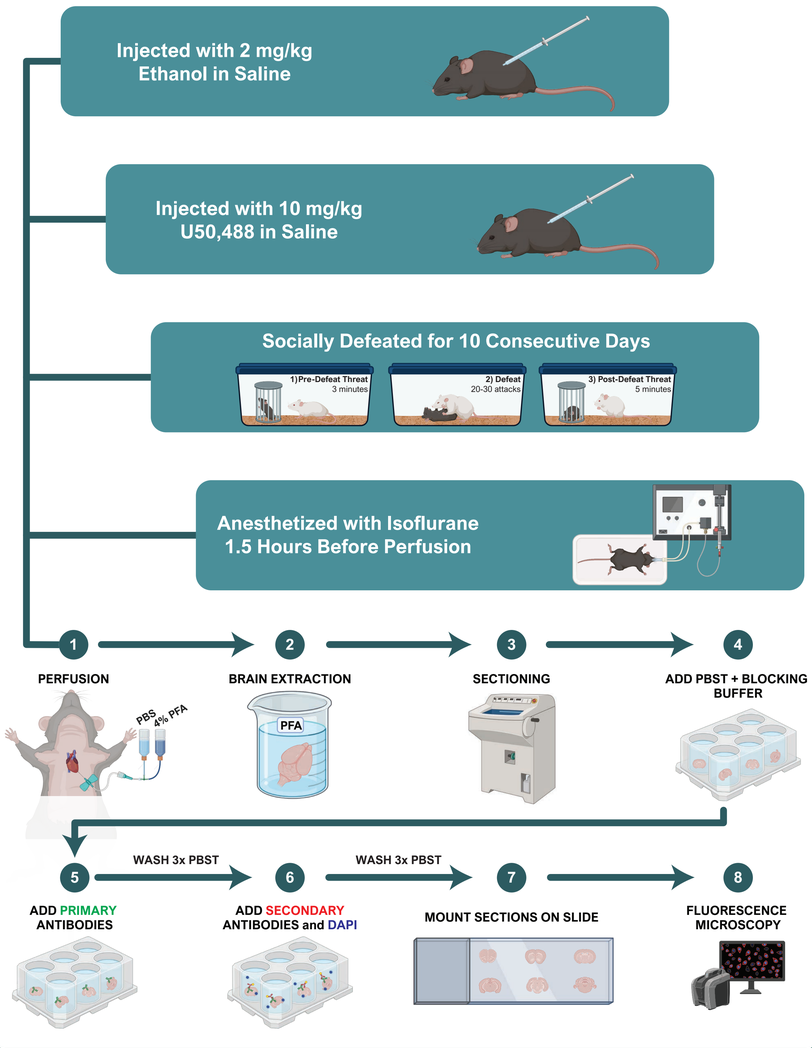
Introduction

- For many years, molecular markers such as Fos have been used to represent neuronal activation, and these markers have been instrumental in physiological research, specifically in the mapping of neuronal circuits
- However, no equivalent marker existed for neuronal inhibition until 2023, when the phosphorylation of pyruvate dehydrogenase (pPDH) was identified as having an inverse correlation with action potential firing intensity in primary neurons
- This relationship allows for the immunostaining of pPDH by monoclonal antibodies to act as a detection method for inhibition across the brain in in vivo mouse models
- pPDH is a revolutionary tool in physiological research, allowing for the recognition of inhibitory pathways that were previously undetectable

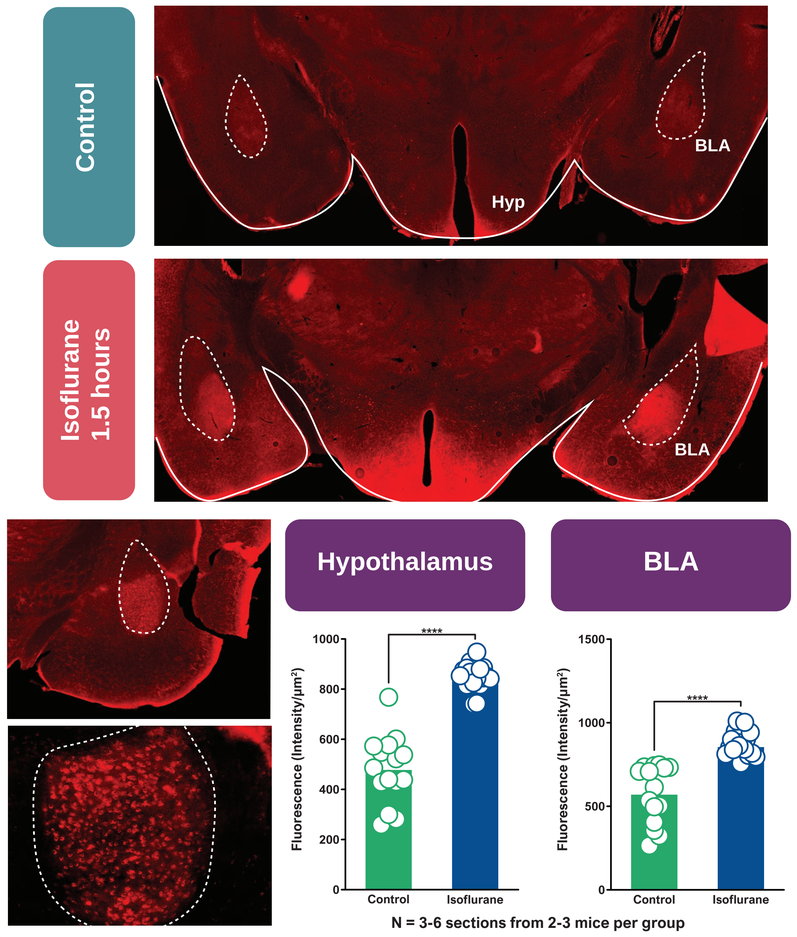
Experimental Background

- This project explores this novel marker's ability to detect neuronal inhibition caused by various modalities including social defeat stress and exposure to isoflurane
- Our lab is interested in understanding neural mechanisms by which repeated social stress leads to increased alcohol consumption
- The current working hypothesis is that stress leads to activation of Dynorphin (Dyn) release from dorsal raphe (DR) Dyn neurons into the bed nucleus of the stria terminalis (BNST)
- The released Dyn then binds to kappa opioid receptors located on basolateral amygdala terminals (BLA) in the BNST leading to neuronal inhibition
- Here, we attempt to visualize this inhibition in BLA neurons after social defeat stress and also after systemic injections of a selective KOR agonist

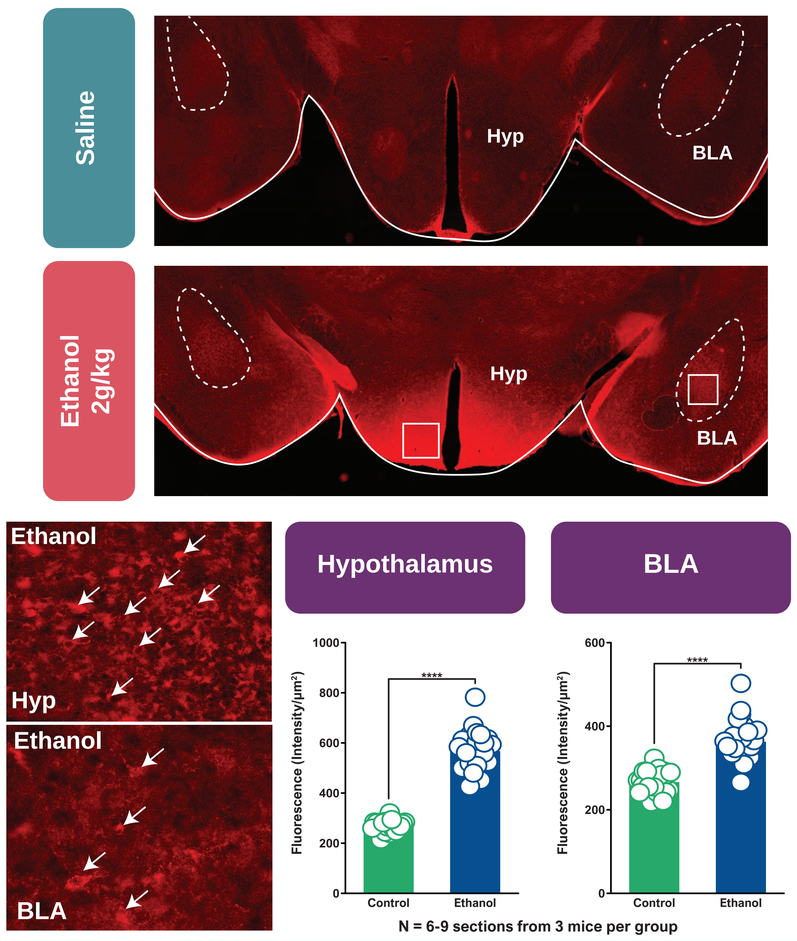
Methods



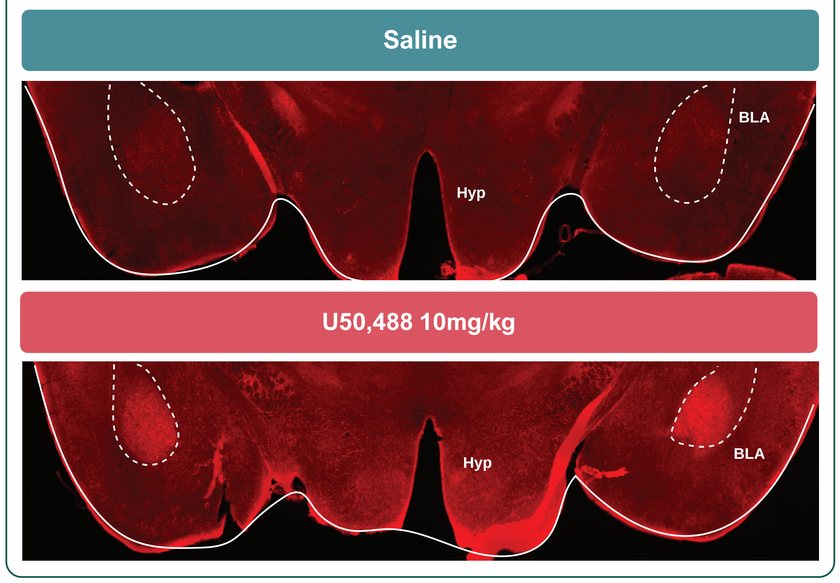
Isoflurane-induced phosphorylation of PDH in the BLA and hypothalamus



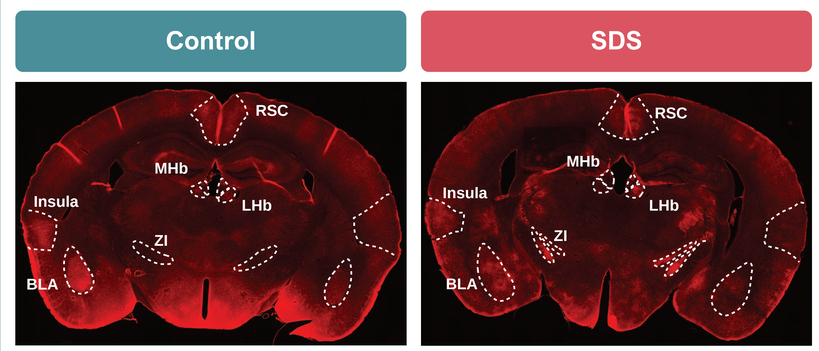
Alcohol exposure enhanced PDH phosphorylation in the BLA and hypothalamus



Administration of κ-Opioid Receptor Agonist U50,488 enhanced phosphorylation of PDH in the BLA



SDS led to unique patterns of pPDH expression in the brain



Summary

- Exposure to isoflurane as well as systemic administration of alcohol (2g/kg)which activate inhibitory $GABA_A$ receptors led to robust pPDH activation in similar brain regions including the basolateral amygdala and several hypothalamic nuclei
- Preliminary results indicate that sysytemic administration of U50,488 increased pPDH in the BLA. However, this effect is less robust compared to alcohol- and isoflurane- induced increases in pPDH and will need to be confirmed in a larger cohort of mice
- Repeated SDS led to a pattern of PDH phosphorylation that was drastically different from the other modalities tested. SDS increased phosphorylation robustly in the Zona Incerta (ZI) and lateral habenula (LHb) which are brain regions important in regulating aggression

The results indicate that pPDH is a useful tool to visualize patterns of neuronal inhibition mediated by a number of strong and weak drivers of neuronal inhibiton

Future studies will follow up on both stress and alcohol-induced increases in PDH phosphorylation