Calcium Imaging of the Nucleus Accumbens Reveals Distinct Physiological Effects of Continuous vs Responsive Neurostimulation

Hemmings Wu MD, PhD; Bina Kakusa BS; Boris D Heifets MD, PhD; Daniel Christoffel; Robert C. Malenka; Casey H. Halpern MD

[Institution]

Introduction

We recently reported that responsive neurostimulation guided by nucleus accumbens (NAc) field potential ameliorates binge eating in mice. However, the mechanism remains unclear, as electrical stimulation artifact complicates signal processing. Here, we utilize, for the first time, in vivo calcium imaging, to record intracellular calcium levels as a proxy for neuronal activity during simultaneous stimulation. Specifically, we used fiber photometry to capture calcium transients in NAc neurons in awake behaving mice to directly assess the physiological differences of continuous and responsive neurostimulation. Our findings are expected to inform stimulation mechanisms not fully appreciated to date.

Methods

AAV-hSyn-GCaMP-6f virus injection, followed by optetrode (fiber optic surrounded by four platinum/iridium electrodes) implantation were performed in the NAc of mice (N=6;male C57-BL6). Mice were then put on a limited (1-hour/day) high-fat exposure protocol known to induce binge-eating behavior. Continuous and responsive neurostimulation (delivered in 10-second epochs) at different

Results

Stimulation delivered at 130Hz significantly ameliorated binge eating. Fiber photometry revealed massive increase in GCaMP fluorescence (>300%), indicative of an increase in intracellular calcium concentration. This increase in GCaMP fluorescence within the NAc lasted roughly 60 seconds with return to baseline despite continuous stimulation for an hour. Responsive stimulation (delivered intermittently) led to a consistent increase during each stimulation epoch. Three and 10Hz stimulation induced minimal change in GCaMP fluorescence with no effect on binges.

Conclusions

Imaging intracellular calcium levels during continuous and responsive neurostimulation revealed distinct physiological mechanisms, though both effectively ameliorate binge eating. This similarity suggests both stimulation protocols can disrupt the role of the NAc in mediating binge eating. Future investigation includes novel correlations across recording modalities to better define the relationship between the calcium fluctuations and neuronal activity.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Described the importance of different mechanisms behind continuous vs responsive neurostimulation revealed by calcium imaging, 2) Discuss, in small groups, how to use calcium imaging technique to investigate the pathological mechanisms of neurological disorders, and the treatment mechanisms of neuromodulation protocols, 3) Identify an effective neuromodulation treatment for neuropsychiatric disorders using calcium imaging.

References