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Optogenetic neuronal stimulation enhances neurotrophin expression in the contralesional motor cortex after stroke

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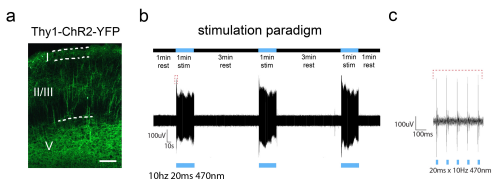
Introduction

Functional recovery after stroke has been observed and is currently attributed to both brain remodeling and plasticity. One form of cortical reorganization involves the balance of interhemispheric interactions between ipsilesional and contralesional cortex. Stimulation of ipsilesional primary motor cortex (iM1) has been shown to be beneficial, however, the role of the contralesional M1 (cM1) remains controversial. Recently we showed that optogenetic stimulations of iM1 post-stroke promote functional recovery. In this study, we investigate the role of contralesional cortex in recovery by optogenetically stimulating iM1 or cM1 and examine the involvement of activity-dependent neurotrophins.

Methods

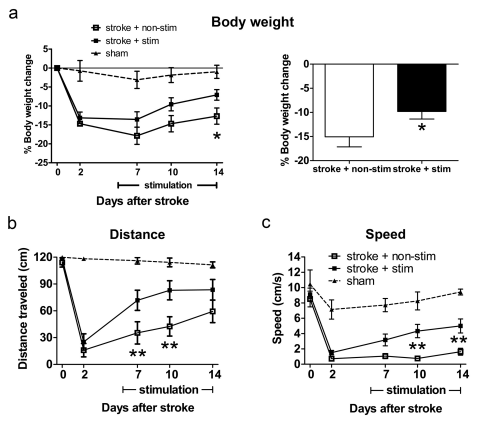
Thy-1-ChR2-YFP line-18 transgenic male mice were used. Mice underwent stereotaxic surgery to implant a fiber cannula in either iM1 or cM1, followed by an intraluminal middle cerebral artery suture occlusion. Optogenetic stimulation began at day5 post-stroke and continued until day14 post-stroke. Sensorimotor behavior tests were used to assess their recovery at day 0, 2, 7, 10 and 14 post-stroke. Mice were sacrificed at day15 post-stroke and neurotrophin expressions were

Stimulation paradigm



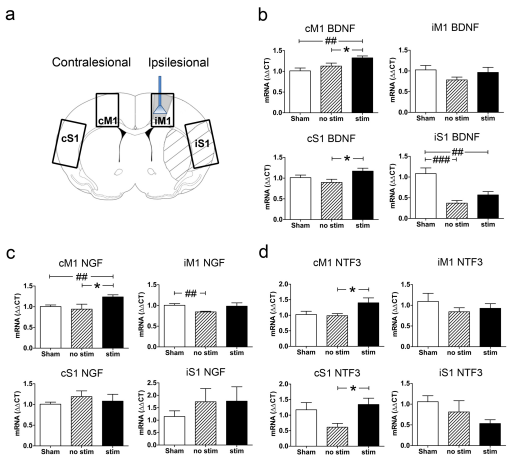
(A) High expression of Thy1:ChR2-YFP in layer V pyramidal neurons of M1. Scale bar = 100 µm. (B) Top, stimulation paradigm with 3 successive 1-min laser stimulations (blue bars) separated by 3-min rest intervals. Bottom, representative optrode tracing of neuronal firings that result from the application of this paradigm to iM1. (C) Enlarged image of a stimulation interval in the optrode tracing of (B), showing individual spiking from the light pulses (red brackets).

Neuronal stimulation promotes functional recovery



Repeated iM1 stimulations promoted functional recovery at day14 post-stroke, with increased weight gain (A) and improved motor performance on the rotating beam test (B, C).

Neuronal stimulation increases neurotrophin expression



Real-time PCR revealed significant increases of neurotrophin expressions in contralesional M1 at day15 post-stroke. (A) Diagram illustrates stimulation site and infarct region. Ipsilesional and contralesional M1 and S1 were dissected. (B) Brain-derived neurotrophic factor (BDNF), (C) nerve growth factor (NGF) and (D) neurotrophin 3 (NTF3) were significantly increased in contralesional M1 (cM1) in stimulated mice after stroke. BDNF and NTF3 expression were also significantly increased in the contralesional S1 of stimulated mice.

Conclusions

Our data suggest that activity-dependent neurotrophins in the contralesional cortex may be an important mechanism mediating stroke recovery. Current studies include specific stimulation and inhibition of the iM1 or cM1 post-stroke to elucidate the neurocircuitry mediating stroke recovery. In addition, the expression of neurotrophins will be examined in these studies to elucidate their role in the recovery process.

Learning Objectives

By the conclusion of this session, participants should be able to understand the importance of neuronal stimulation on functional recovery after stroke, and learn the involvement of neurotorphins in recovery. The participants will also learn that optogenetics is a good tool to study recovery after stroke, as well as a potential brain stimulation technique that targets specific cell types.