Proliferation in the Adult Mouse Brain Following Distal Middle Cerebral Artery Occlusion

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Introduction

The adult brain possesses an innate ability to generate new neurons from dividing neural precursor cells (NPCs) during the process of neurogenesis (Ming and Song, 2011). After a stroke, there is a dramatic increase in the number of diving NPCs (Lagace, 2011). These new NPCs do not result in increased functional recovery post stroke since most of the NPCs die and do not generate new neurons. Thus, preclinical research is required to determine how neurogenesis can be enhanced in order to help stroke survivors.

Preclinical studies using Middle Cerebral Artery occlusion (MCAo) model demonstrate that MCAo induces proliferation of NPCs and ectopic migration to the site of injury (Kernie and Parent, 2010). It is difficult to translate these findings into human populations since this model produces substantial infarcts that are larger than those observed in humans (Carmichael et al 2005).

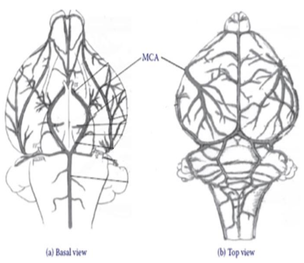
This study determines how NPCs are affected by a Distal Middle Cerebral Artery occlusion (dMCAo) that produces infarcts of similar size to that occurring in humans. Based on the MCAo findings and one paper examining outcomes following MCAo (Shimida et al. 2010), we hypothesized that dMCAo will increase the number of dividing NPCs and induce ectopic migration to the site of injury.

Methods

Adult male mice received either dMCAo (n=8) or sham (n=7) surgery.

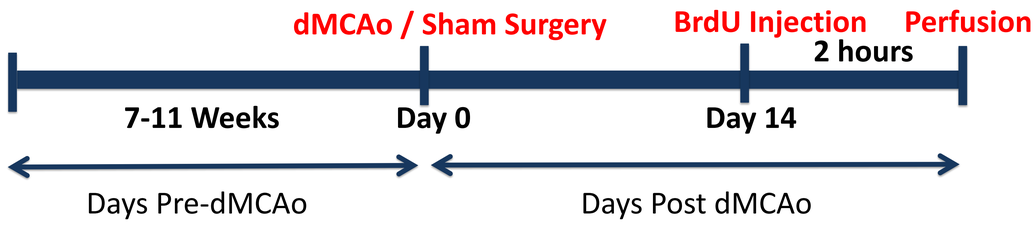
Bromodeoxyuridine (BrdU) was injected 2 hours before perfusion in order to label proliferating cells.

Brain tissue was cut on a microtome, and the brain sections were used for immunohistochemistry (IHC). All sections were analyzed blind to condition, and co-labeling was determined using the confocal microscopy.



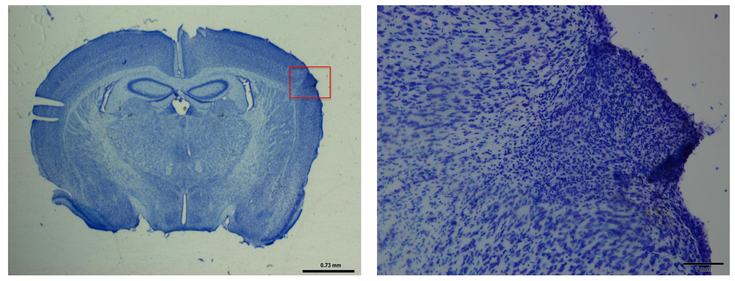
Prado, Wang Fischer, Koetzner (2008)

Experimental Timeline

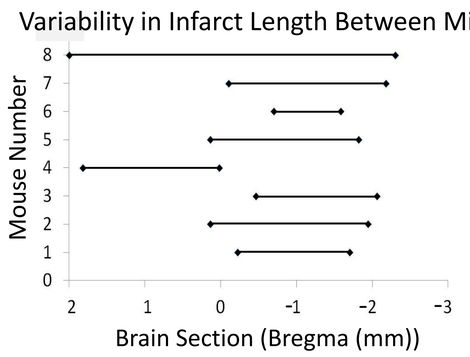


Results

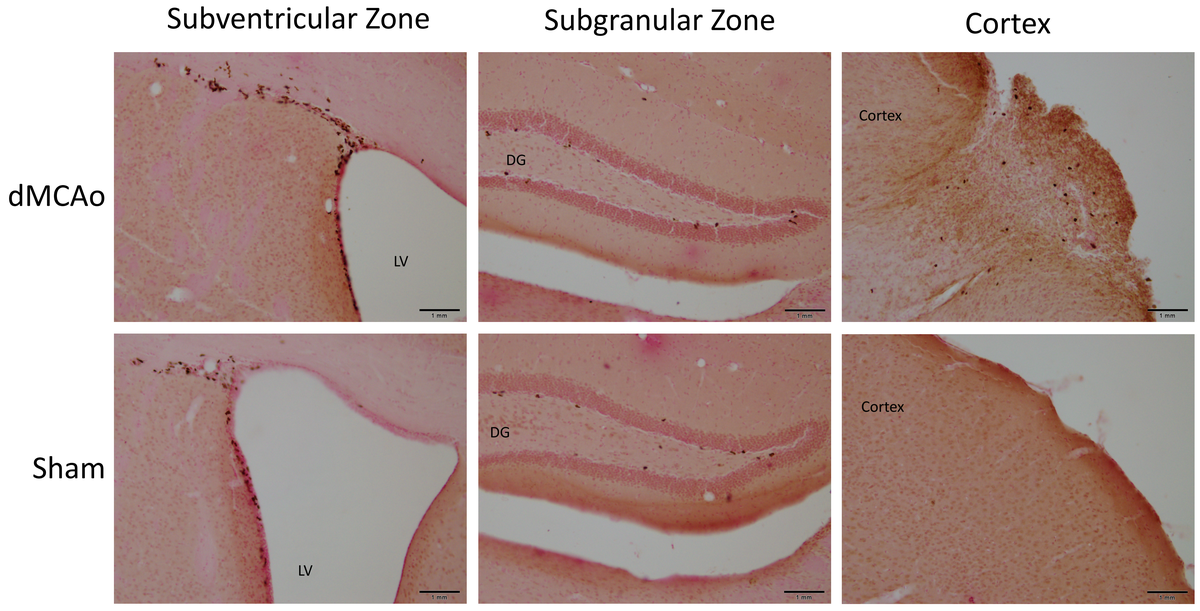
Infarct Volume Determined using Cresyl Violet Staining



Representative cresyl violet staining of dMCAo tissue at low (left) and at high (right) magnification. The infarct was localized mostly to the somatosensory cortex.

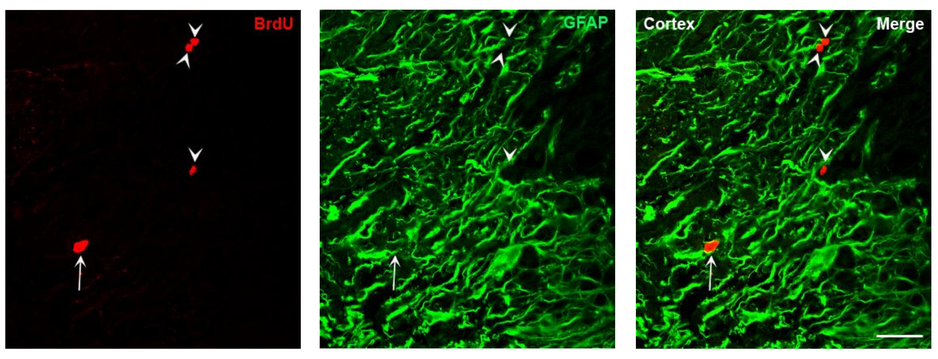


BrdU labeled Cells in dMCAo and Sham Mice



Representative images of BrdU labeled cells (brown cells identified by IHC detection) in the subventricular zone (SVZ) and the subgranular zone (SGZ) in both dMCAo and sham mice. dMCAo mice also had BrdU-labeled cells in the area of the cortical infarct.

~8% of BrdU Labeled Cells in the dMCAo Infarct Region Expressed The Astrocytic Protein GFAP



Representative image of BrdU labeled cells that do not express GFAP (arrowhead) or express GFAP (arrow) as determined by confocal analysis. Scale Bar: 20 mm.

Summary

- dMCAo stroke surgery in mice induced infarcts primarily in the somatosensory cortex.
- The dMCAo infarcts were fairly consistent between mice with 5/8 exhibiting a similar location of infarct with a length of less than 2mm.
- Cell proliferation, identified by BrdU labeling, was observed in the neurogenic regions of the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus.
- BrdU labeled cells were observed in the region surrounding the infarct in only the dMCAo mice.
- Very few BrdU labeled cells had an astrocytic phenotype and expressed GFAP.

Future Direction

In order to understand if proliferation of NPCs changes following dMCAo, we need to quantify if there is a difference in the number of BrdU labeled cells in SVZ or SGZ in dMCAo versus sham mice. We also want to determine what type of cells are labeled with BrdU in the cortex following dMCAo. These results will help us determine how proliferation may be changing in the adult brain following a stroke.

References

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