Combined Treatment Strategy to Enhance Neurogenesis After Stroke

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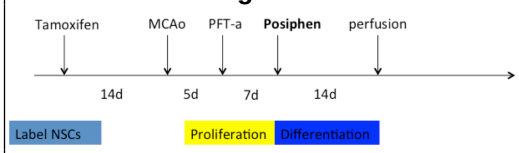
Introduction

Recently, a role for amyloid-ß protein precursor (APP), best known for its role in Alzheimer's disease (AD), has been implicated in synapse formation, neural plasticity, and the differentiation of neural stem cells. To enhance the neuronal differentiation of endogenous progenitor cells, we utilized an APP inhibitor, (+)-phenserine (posiphen), in combination with PFT-a to study the response of endogenous neural progenitor cells and functional recovery in an animal stroke model, middle cerebral artery occlusion (MCAo). Utilizing a specific p53 inhibitor (PFT-a), our group has enhanced the proliferation and survival of endogenous progenitor cells in-vivo, leading to enhanced functional recovery in stroke animals days and weeks after stroke onset. In this study, our data shows that combined treatment with PFT-a and posiphen resulted in increased proliferation and differentiation of neuronal stem cells in the subventricular zones (SVZ) of combined treatment mice, yielding decreased cognitive deficits and improved functional recovery compared to vehicle treated mice.

Methods

Mice were separated into two groups, with the treatment group receiving 7 days of PFT-alpha at psd 5 followed by 14 days of posiphen administration. The control group received DMSO and saline respectively at these same time points. The mice underwent pre-stroke locomotion testing that was repeated weekly to follow recovery. Before perfusion, all animals underwent novel object recognition testing, carried out over successive days, and Rotarod testing to evaluate cognitive recovery. All animals underwent perfusion and immunohistochemical staining.

Figure 1

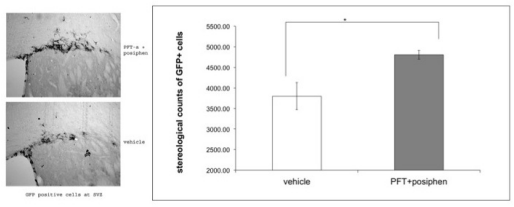


Experimental Timeline

Results

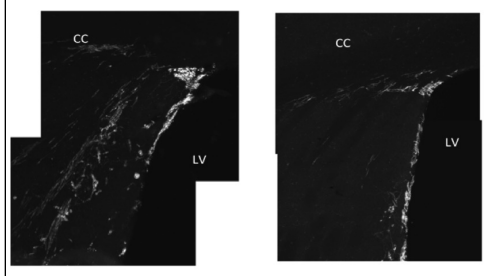
The behavioral tests, spontaneous locomotion and RotaRod, as well as the cognitive testing showed an improved functional recovery in the treatment group. Our results also show that PFT-alpha administration resulted in a significant increase in the number of sub-ventricular zone (SVZ) and sub-granular zone (SGZ) neuronal stem cells. Additionally, combined treatment of PFT-a and (+)-phenserine resulted an increase in immature neuroblasts present post-infarct, indicating enhanced neuronal differentiation.

Figure 2



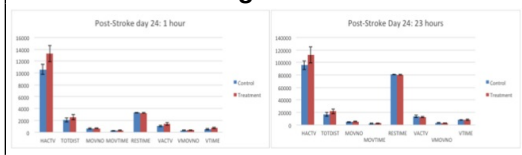
GPF+ staining of SVZ shows statistical increase of neuronal stem cells in combined treatment mice

Figure 3



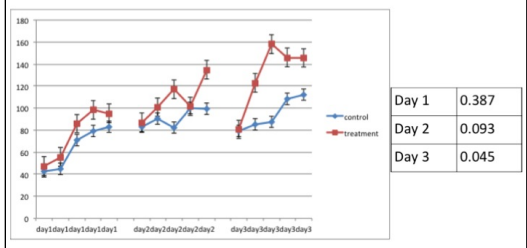
DCX staining shows increase in immature neuroblasts both at SVZ and migrating to site of infarction

Figure 4



Locomotion data from post-stroke day 24 showing a statistically significant ($p < 0.05$) improvement in activity in the combined treatment mice versus control.

Figure 5



Novel object recognition data showing a statistically significant increase in the ratio of preference of the novel object in both total duration and frequency of investigation

Learning Objectives

By the conclusion of the session, participants should be able to: 1) Understand the effect of p53 and APP on neuronal stem cells. 2) Recognize the potential of neuronal stem cells to affect recovery post-stroke.

References

Luo Y, Kuo C-C, Shen H, Chou J, Greig NH, Hoffer BJ, et al. Delayed treatment with a p53 inhibitor enhances recovery in stroke brain. Annals of Neurology, 2009:9999(999A):NA.

Aydin D, Weyer SW, Muller UC. Functions of the APP gene family in the nervous system: insights from mouse models. Exp Brain Res, 2011.

Conclusions

-Combined treatment with PFT-alpha and posiphen results in an increase in the number of neuronal stem cells present at the SVZ and the differentiation and migration of NSCs to the site of injury

-Post-stroke treatment of results in increased functional and cognitive recovery

These findings suggest that combined treatment with a p53 inhibitor and APP inhibitor can lead to increased functional and cognitive recovery post-MCAo through increased proliferation and differentiation of NSCs. This treatment strategy may provide a novel pathway for improvement in functional recovery following ischemic stroke.