Functional Modulation of the Blood Brain Barrier

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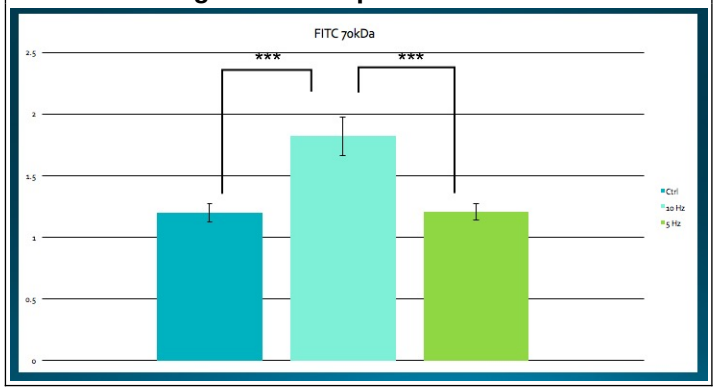
Introduction

Delivery of therapeutic agents to the brain is constrained by the blood-brain barrier (BBB). Previous work (Yarnitsky) suggested BBB permeability was increased with stimulation of the sphenopalatine ganglion (SPG). However, their model looked at FITC-dextran signal in CSF superfusate, a reflection of epithelial tight junctions at the blood-CSF barrier, and quantified BBB permeability using Evans blue, a marker insufficient for this role (Saunders).

Methods

Experiments were conducted in Sprague-Dawley rats using 70kDa FITC-dextran as a marker to quantify BBB permeability. Once anesthetized, the right femoral vein was exposed and catheterized. Next, SPG fibers were exposed behind the right eye and an electrode was hooked around those fibers. Stimulation occurred in blocks of 90 seconds of "on" time at 5 volts and 10Hz followed by 60 seconds of "off" time. Injection of 0.1mL of a 100mg/mL concentration of FITC coincided with each "on" stimulation cycle; a total of 1.0mL was injected per animal. Control animals underwent placement of the electrode but were not stimulated, however they did have the same injection protocol as test animals. A third group of animals was stimulated at 5Hz with a protocol otherwise identical to those stimulated at 10Hz. 90 seconds after the final injection, a blood sample was collected and the cerebrovasculature was flushed. Each brain was removed, equally divided, and homogenized. Post-centrifugation supernatant from blood and tissue homogenates was analyzed using fluorescent spectrometry. FITC concentrations were calculated using known standards. An uptake ratio was calculated by dividing sample FITC concentration by blood FITC concentration.

Average Percent Uptake: Whole Brain



Results

Data from six control animals, six 10Hz stimulation test animals, and four 5Hz stimulated animals were compared. Stimulation at 10Hz causes significantly greater uptake of FITC compared with control conditions ($p=0.0005$) and 5Hz stimulation ($p=0.0009$). A significantly increased uptake ratio was also observed in both right and left hemispheres of the 10Hz stimulated animals compared with controls (right, $p=0.034$; left, $p=0.001$). and 10Hz compared with 5Hz stimulated animals (right, $p = 0.046$; left, $p = 0.004$).

Conclusions

Stimulation of SPG fibers at a frequency of 10Hz significantly increased BBB permeability in both cerebral hemispheres of test animals when compared with control animals and animals stimulated at a frequency of 5Hz.

Learning Objectives

By the conclusion of this session, participations should be able to:

1. Describe the anatomic basis of the blood-brain barrier

2. Discuss the role of SPG stimulation in increasing blood-brain barrier permeability

3. Discuss the role of SPG stimulation in improving existing therapeutic modalities

References

Yarnitsky D, Gross Y, Lorian A, et al. Blood-brain barrier opened by stimulation of the parasympathetic sphenopalatine ganglion: a new method for macromolecule delivery to the brain. J Neurosurg. 2004;101:303-309.

Saunders N, Dziegielewska K, Mellgard K, Habgood M. Markers for blood-brain barrier integrity: how appropriate is Evans blue in the twenty-first century and what are the alternatives? Front Neurosci. 2015;9.

Average Percent Uptake: Right Brain vs. Left Brain