In-vivo performance of a microfabricated catheter for intraparenchymal delivery

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Introduction

Convection-enhanced delivery (CED) is an effective technique to bypass the blood-brain barrier (BBB) and deliver drugs directly into the brain parenchyma. However, several technical limitations must be addressed to increase its efficiency, repeatability, and effectiveness in clinical practice.

Microfabricated Catheter

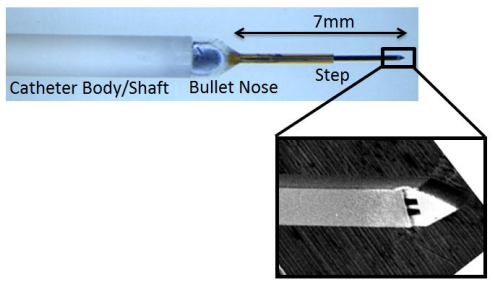

Fig 1. Micro-Electro-Mechanical-Systems (MEMS) Tip with features to stop backflow

Methods

This study reports infusions of tracers of various sizes into the brain of a large mammal (pig) using a novel microfabricated catheter. Standard stereotactic procedures were used to target the anatomy. Infusions through the microcatheter at various infusion rates were evaluated for possible backflow or reflux up the outside of the catheter, which has proved to be a problem in CED infusions, especially at high infusion rates. Each pig was infused bilaterally, with a total of 3 White Matter, 3 Putamen, and 3 Thalamus infusions to assess backflow.

Real time magnetic resonance (MR) imaging was used to examine the distributions of the tracers and their concentration profiles in the parenchyma. In-line catheter pressures were monitored for all infusions. Infusions were carried out in porcine white matter, thalamus, and putamen.

Results

The extent of backflow, if any, and concentration profiles were determined for several MR contrast reagents and fluorescent dyes with sizes that are typical of small molecules, therapeutic proteins and an adeno-associated virus (AAV). Infusion flowrates up to 40 µl/min were achieved without evidence of backflow of infusate along the catheter. The ratio of the volume of distribution in tissue to the infusion volume (Vd/Vi) was similar for all infused reagents. The 2x independent channels were demonstrated by infusing Gd from the first channel, and dye from the second channel. The in-line pressures were consistent with theoretical values for flow through a micro-lumen.

White Matter Infusions to Assess Backflow

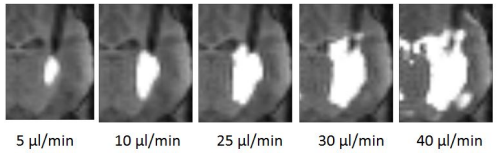

Fig 2. MR images of Gadolinium infusions into Porcine White Matter, at increasing flowrates

Thalamus Infusions to Assess Backflow

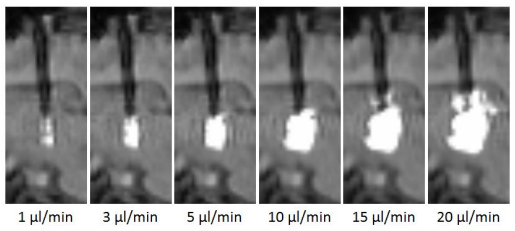

Fig 3. MR images of infusions into Porcine Thalamus, at increasing flowrates

Putamen Infusions to Assess Backflow

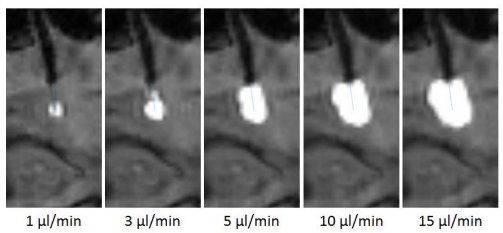

Fig 4. MR images of infusions into Porcine Putamen, at increasing flowrates

Vd/Vi Curves for Various Reagents

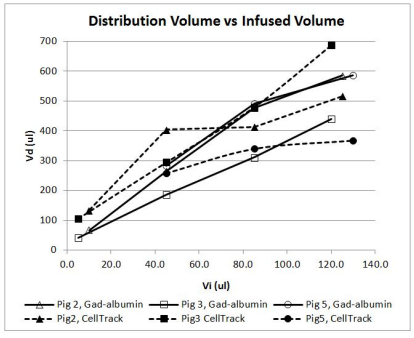

Fig 5. Gd-albumin in Thalamus, CellTrack (an AAV-size colloidal-Gd molecule) in White Matter

Two Different Reagents Infused from Two Independent Channels

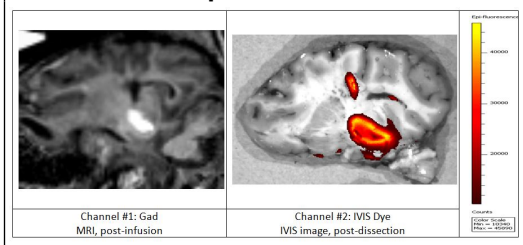

Fig 6. IVIS dye (infused from independenct channel #1) distribution compared to Gad (infused from independenct channel #2) MRI distribution.

White Matter Infusions to Quantify Distribution Gradient

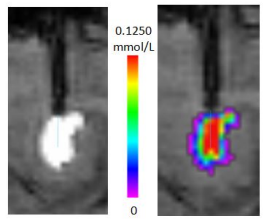

Fig 7. Colloidal Gadolinium distribution in Porcine White Matter after 17 minutes of infusion at 5 µl/min.

Conclusions

The microfabricated catheter was able to target different cytoarchitectures with precision using standard functional stereotactic techniques, and deliver small and large molecules at high infusion rates without evidence of backflow. The measured distribution volumes indicated that all infusates were readily convected through the interstitial space regardless of molecula size.

Reference

Brady el al. J. Neuroscience Methods. 229 (2014) 76-83