In situ delivery of trophic factors and molecules in the human brain by convection technologies.

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Convection-enhanced delivery (CED) is a direct method of distribution for therapeutic agents within the central nervous system (CNS) that bypasses the blood-brain barrier (BBB). CED allows the homogenous distribution of a variety of molecular species within the CNS extracellular space (ECS) by developing a pressure gradient between the tip of the infusion catheter and the surrounding ECS [1]. The propagation of therapeutic materials within the resulting bulk flow of infusate is not size dependant, as it is for delivery technologies that are based upon diffusion. This fact allows the transmission of macromolecules and viruses in addition to small molecular species within the CNS via CED [2-5].

Our laboratory has been actively involved in developing a delivery platform that combines MRI and CED technologies (real-time convective delivery, RCD) [6]. We currently utilize RCD for our preclinical investigations and stress the importance for its use in clinical applications for neurodegenerative diseases [7], neuro-oncology [8], and inherited metabolic disorders [9] affecting the CNS, since it allows us to directly monitor the infusion of therapeutics within the target site. This direct visualization may not only help improve treatment efficacy for a therapeutic, by standardizing the volumetric distribution, but is also important in preventing reflux and leakage associated with CED [10].

In this presentation, we aim to review the how CED technologies function and how they may impact future treatments of human brain disorders.

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Figure

Figure 1. Cannula-based Delivery Options Utilized with Gene Therapy

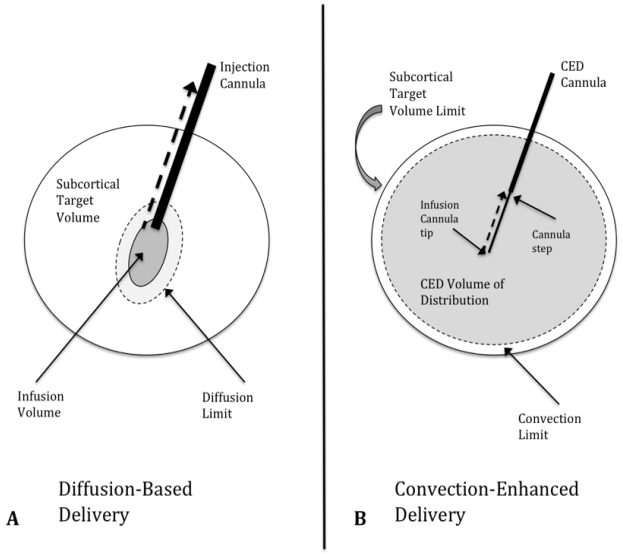

Figure caption

(A) Diffusion-based delivery system: A characteristically large injection cannula is used to deliver the infusion volume within the target region. The infusion volume typically displaces the surrounding parenchyma at the tip of the cannula and forms a small cavity from which diffusion occurs into the surrounding brain, eventually expanding to the diffusion limit, but falling significantly short of filling the subcortical target volume. Multiple factors influence the diffusion limit for infused substances, with molecular size being one of the most significant factors. Macromolecules, proteins and viral particles are limited significantly in their ability to diffuse beyond the infusion volume. Another factor that limits the effectiveness of this technique is the development of backflow or reflux (dashed black arrow) of the infusate out of the target region, along the path of the injection cannula. (B) Convection-enhanced delivery (CED) system: Optimal CED cannulae consist of an outer guide cannula and an inner fused-silica infusion cannula that is attached to the pump mechanism that controls the rate of infusion. The infusion cannula extends beyond the guide cannula, with the transition between the two referred to as the cannula step. The infusate is delivered with a constant flow rate (most commonly 0.5 to 1.0 µl/min) from the infusion cannula tip. This flow rate establishes a pressurized extracellular bulk flow that allows the homogenous distribution of molecules of various sizes, including liposomes, proteins and viral particles, for significant distances (multiple centimeters, if necessary) from the infusion cannula tip. Reflux (dashed black arrow) typically only occurs up to the cannula step, and major backflow along the cannula and out of the target region is prevented by central placement of the step within the target volume. The convection limit can approach the subcortical target volume limit more easily compared with the diffusion-based delivery system.

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