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REVIEW

Convection-Enhanced Drug Delivery to the Brain: Therapeutic Potential and Neuropathological Considerations

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Abstract

Convection-enhanced delivery (CED) describes a direct method of drug delivery to the brain through intraparenchymal microcatheters. By establishing a pressure gradient at the tip of the infusion catheter in order to exploit bulk flow through the interstitial spaces of the brain, CED offers a number of advantages over conventional drug delivery methods—bypass of the blood–brain barrier, targeted distribution through large brain volumes and minimization of systemic side effects. Despite showing early promise, CED is yet to fulfill its potential as a mainstream strategy for the treatment of neurological disease. Substantial research effort has been dedicated to optimize the technology for CED and identify the parameters, which govern successful drug distribution. It seems likely that successful clinical translation of CED will depend on suitable catheter technology being used in combination with drugs with optimal physicochemical characteristics, and on neuropathological analysis in appropriate preclinical models. In this review, we consider the factors most likely to influence the success or failure of CED, and review its application to the treatment of high-grade glioma, Parkinson's disease (PD) and Alzheimer's disease (AD).

INTRODUCTION

Convection-enhanced drug delivery (CED) describes the direct infusion of drugs into the brain parenchyma through microcatheters (9). By using highly controlled flow rates to establish a pressure gradient at the tip of the infusion catheter, this technique allows drugs that do not cross the blood–brain barrier (BBB) to be delivered in therapeutic concentrations throughout large volumes of brain tissue, while minimizing systemic exposure. CED also has application for the delivery of drugs that cause intolerable or unwanted side effects when administered systemically at concentrations required to cross the BBB.

CED differs from traditional methods of intraparenchymal drug delivery, which usually involve the injection of agents into the brain and rely upon simple diffusion into adjacent tissue along a concentration gradient (Figure 1A). The "convective" nature of CED reflects the fact that infusates carried by a pressure gradient will reach distances approximately proportionate to the duration of infusion, whereas an agent carried by diffusion will reach distances proportional to the square root of the time elapsed.

The concept of pressure-mediated intraparenchymal drug infusion was first described in the early 1990s, but is yet to fulfill its potential as a mainstream therapeutic strategy for neuro-oncological and neurodegenerative diseases. Extensive preclinical and early clinical studies have demonstrated that effective CED depends upon a number of parameters—the diameter of the catheter, the catheter implantation method, the rate of infusion, the physicochemical characteristics of the infusate, and the cytoarchitecture of the targeted brain tissue or structure.

Successful clinical translation of CED is likely to require an in-depth understanding of all of these parameters, as well as the use of appropriate preclinical models and detailed neuropathological and neuroradiological analysis of drug effect and distribution. In this review, we consider the factors that are most likely to influence the success or failure of CED, and review its application to the treatment of high-grade glioma, Parkinson's disease (PD) and Alzheimer's disease (AD).

CATHETER TECHNOLOGY AND IMPLANTATION METHODS

One of the major barriers to effective clinical translation of CED is the incidence of infusate reflux or "backflow" along the catheter/brain interface. Reflux reduces the chances of achieving therapeutic drug concentrations in the target structure and increases the risk of off-target side effects. The deleterious consequences of infusate

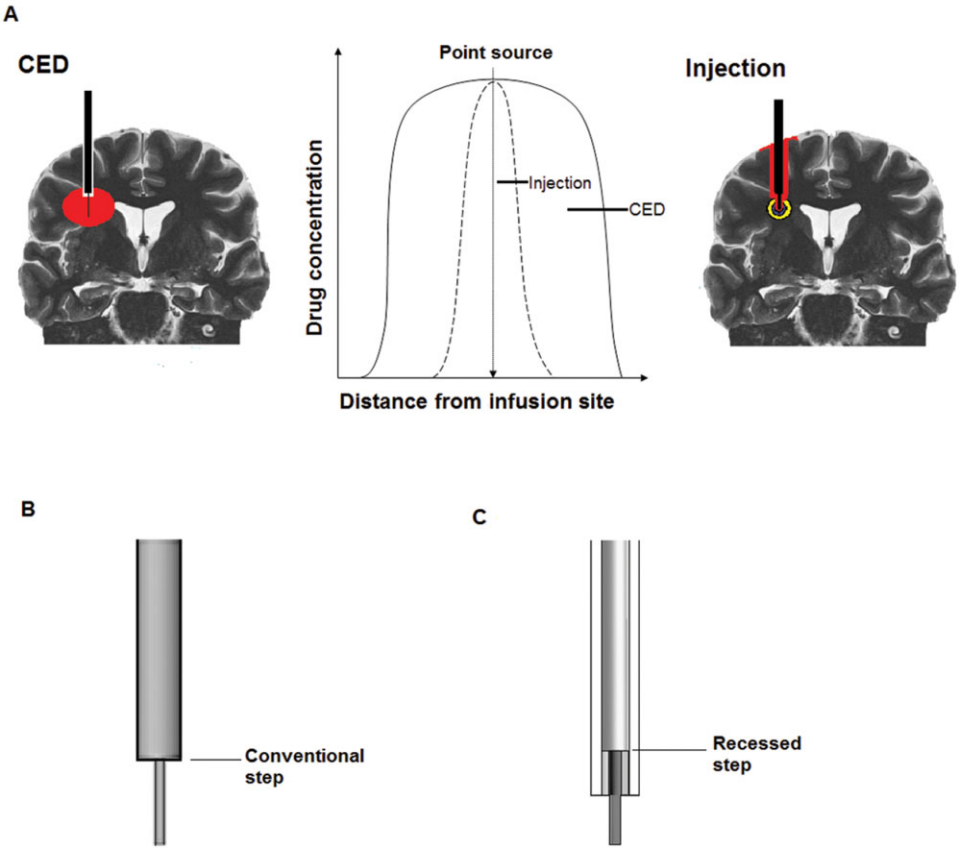

Figure 1. A. Convection-enhanced delivery differs in both technique and technology from conventional methods of drug injection. By use of ultrafine microcatheters, minimally traumatic implantation techniques and highly controlled infusion rates, CED facilitates homogeneous drug distribution through large, clinically relevant brain volumes. In contrast, local injection methods are associated with significant reflux of drug, tissue trauma and inhomogeneous drug distribution, which is reliant on diffusion rather than bulk flow through the interstitial spaces of the brain. **B.** Conventional "stepped" catheter designs incorporate an abrupt change in catheter diameter proximal to catheter tip which acts to reduce reflux. **C.** We recently described a novel "recessed-step" catheter in which the stepped element is held within an outer guide tube.

reflux were clearly demonstrated in clinical trials of CED of paclitaxel for high grade brain tumors, which was associated with leakage of the drug into the subarachnoid spaces and chemical meningitis (45).

Preclinical studies have identified three parameters relating to catheter design and implantation method, which significantly increase the risk of reflux—catheter diameter, tissue trauma on catheter implantation and the speed of catheter insertion. Chen *et al* (16) were the first to analyze systematically the effect of catheter diameter on the incidence of reflux, and correlated smaller catheter diameter with reduced reflux. It seemed likely that larger bore catheters cause more tissue trauma on implantation, reducing the effectiveness of the seal at the catheter/brain interface. This hypothesis was tested and confirmed in subsequent preclinical and clinical studies, which found effective drug distribution in the target structure to be achievable with catheters less than 1 mm in diameter (56, 90). CED studies in agarose brain phantoms correlated reduced reflux with increased speed of catheter implantation—an effect also likely to be mediated by reduced "tissue" displacement on catheter insertion and consequently reduced trauma away from the catheter itself (15).

A further refinement was the introduction of "stepped" catheters, which facilitate high-flow infusions without reflux (39, 92). A stepped catheter incorporates an abrupt change from a large to a small diameter proximal to the catheter tip (Figure 1B). A stepped catheter design was used to good effect in clinical trials delivering virally mediated gene therapy into the putamen for the treatment of PD (18). The mechanisms by which a step reduces the risk of reflux are not fully understood but are likely to be related to the complex relationship between focal compression of tissue to create a seal, and reductions in the hydrostatic pressure of infused fluids. We recently described a novel "recessed-step" catheter, which incorporates a step internalized within an outer guide tube and has been used to deliver high-volume, high-flow rate infusions into a brain stem glioma without evidence of reflux (6) (Figure 1C). This "recessed-step" design showed superior reflux resistance to a conventional stepped catheter, both *in vitro* and *in vivo* in a large animal (porcine) model (23).

Figure 2. *Intermittent delivery of non-gene therapies may be necessary for drugs with relatively short biological or tissue half-lives.* We recently developed an implantable CED catheter system, which facilitates chronic intermittent drug delivery to the brain through a transcutaneous bone-anchored port.

INFUSATE CHARACTERISTICS

The distribution of a drug delivered to the brain by CED is fundamentally reliant upon the physicochemical properties of the infused agent. By employing a pressure-mediated infusion regime, CED aims to exploit bulk flow through the interstitial spaces of the brain. This potentially allows infused agents over a wide range of molecular weights, including particles and viral constructs, to be distributed effectively within the brain (9, 17, 41, 55).

The surface properties, and resultant tissue affinity, of the infused molecule appear to be far more important than molecular weight in influencing the extent of distribution in the brain (17). For example, cationic liposomes do not distribute effectively in the brain when delivered by CED because of their inherent affinity for the cell membrane (49, 69). Shielding the positive charge of cationic liposomes to confer either neutrality or anionic charge significantly improves distribution (37, 49, 69).

The presence of tissue-binding moieties within the structure of an infused molecule is also a significant determinant of distribution. Both adeno-associated virus serotype 2 (AAV2) and glial cell line-derived neurotrophic factor (GDNF) contain heparin-binding sites, which have an affinity for the heparan sulfates of the extracellular matrix within the brain. Co-infusion of heparin was shown to improve the distribution of both AAV2 and GDNF in preclinical studies, by competitively binding the receptors (28, 59). The accumulation of amyloid-β (Aβ) in the extracellular spaces of the brain in AD, *en route* from neurons to blood vessels, presumably reflects constraints similar to those preventing the distribution of molecules with high tissue affinity by CED (88, 89).

It seems likely that particulate therapies that are neutral or anionic, and hydrophilic molecules with low tissue affinity will be most effectively distributed in the brain by CED. However, these same characteristics may hamper their translational potential by resulting in rapid interstitial clearance from the brain—a problem we encountered in preclinical studies of CED of neprilysin (see below) (5). The tissue half-life of drugs delivered to the brain by CED was reported to be as short as 7 h, which introduces a potential need for intermittent drug delivery and implantable CED catheter systems (2). We recently described the development of an implantable CED system, which facilitates chronic intermittent drug delivery to the brain at intervals determined by the tissue and biological half-life of the infusate, through a transcutaneous bone-anchored port (7) (Figure 2).

INFUSION RATES AND RAMPING REGIMES

The ability to tightly control and titrate the rate of infusion is fundamentally important for successful CED. In two of the earliest analyses of the effect of infusion rate on distribution, higher flow rates (1 and 5 μL/minute) were associated with significantly greater reflux (16, 54). However, these early studies predated the use of stepped catheters, which have been effective in inhibiting reflux in large animal preclinical and clinical studies at flow rates of up to 10 μL/minute (6, 8, 23, 93). The facility to use relatively high flow rates is of paramount importance for clinical translation because high flow rates offer the potential to limit the duration of infusions to timescales, which are acceptable to patients, without compromising volumes of distribution. There is, however, a balance between using high infusion rates and increasing the risk of trauma because of excess pressure at the catheter tip. The maximum safe infusion rate for CED is currently under investigation and is likely to be dependent upon the diameter of the catheter used, as well as the nature of the target structure in the brain (gray matter, white matter or tumor).

The use of ramping regimes (slow, stepwise increases in infusion rate) has been postulated to reduce the risk of reflux and enhance distribution by inducing gradual expansion of the extracellular spaces of the brain (4, 76). Although no comprehensive comparison of ramped and nonramped infusion regimes has been reported, there is some anecdotal evidence from preclinical studies, which supports the use of ramping in clinical trials (8).

INFLUENCE OF THE PERIVASCULAR SPACES AND CYTOARCHITECTURE OF TARGETED BRAIN REGIONS

The relationship between the perivascular (Virchow–Robin) and subarachnoid spaces of the brain has been determined from histological, ultrastructural and tracer studies. The pia mater is reflected from the surface of the human brain on to the outer aspect of arteries and veins in the subarachnoid space, thereby separating the subarachnoid space from the subpial space and from perivascular spaces in the brain by a thin sheet of pial cells. A layer of pia mater coats arteries as they enter the brain and separates the artery wall from the surrounding brain (30, 31). The concept of "paravascular" fluid drainage through the brain arose from experimental evidence that demonstrated the rapid transit of tracers in cerebrospinal fluid (CSF) throughout the brain in parallel to the cerebral microvasculature (25, 66). By infusing horseradish peroxidase protein tracer into the CSF of cats and dogs, Rennels *et al* (67) were able to demonstrate consistent distribution throughout the perivascular space in association with large vessels, arterioles, capillaries and venules. The rapid transit of tracer could be completely abolished by occluding the aorta or brachiocephalic artery, which resulted in reduced cerebral artery pulsatility. Rennels *et al* (66) concluded that the apparently convective nature of fluid drainage was mediated by transmission of arterial pulsations through the perivascular space.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) offered an ultrastructural insight into the relationship of the perivascular spaces to the microvasculature (1, 64, 94). Pollock *et al* (64) compared the ultrastructural anatomy of the human anterior perforated substance and basal ganglia with that of the cerebral cortex, and identified differences in the relationship of the perivascular space to the vasculature in these regions of the brain. In the anterior perforated substance, the inner layer of the leptomeninges was closely related to the adventitia of the vessel wall, while the outer layer was continuous with the cortical pia mater. In contrast, arteries in the basal ganglia were surrounded by two leptomeningeal layers separated by a perivascular space, which is continuous with the perivascular space around arteries in the subarachnoid space, but not with the subarachnoid space itself (64).

To optimize therapeutic drug delivery by CED, it is necessary to understand fully the ultrastructural anatomy and physiology, which govern the dynamics of fluid flow through the interstitial and perivascular spaces. Early *in vivo* studies of CED attributed the distribution of macromolecules to interstitial flow and neuronal transport (40, 46, 96). However, as research progressed to include the delivery of liposomes and viral vectors, it became clear that much of the distribution of agents delivered by CED was in close association with blood vessels and perivascular spaces (38, 86).

To test the hypothesis that CED relies upon cerebrovascular pulsatility to drive infused agents through the perivascular space, Hadaczek *et al* (27) designed an experiment to assess whether manipulation of cardiovascular parameters would alter the volume of distribution of agents delivered by CED. In their study, a viral vector, liposomes and bovine serum albumin were delivered into the striatum in three groups of rats—a normotensive group, a hypertensive group treated with epinephrine and a no-heartbeat third group in which the animals were euthanized immediately prior to infusion. The volume of distribution was up to 14 times higher in the hypertensive than the no-heartbeat group. This study also concluded that the most informative cardiovascular parameter was pulse pressure, which correlated most significantly with the distribution of infused agents.

In vivo real-time magnetic resonance imaging (MRI) of CED has offered further insight into the importance of the perivascular space in the distribution of molecules delivered by CED, particularly to the basal ganglia (38). Krauze *et al* delineated a distinct putaminal perivascular pathway by real-time MRI of liposomal CED in primates (38), and postulated that variation in perivascular ultrastructure could explain the differences in drug distribution seen when CED is targeted to the putamen compared with targeting of white matter and cortex. Certainly, this variation in ultrastructure has been identified by previous studies (64). We found that intrastriatal CED of model solutes results in rapid and widespread perivascular distribution and uptake by perivascular macrophages, irrespective of molecular weight, co-infusion of vasodilators and infusion regime (4) (Figure 3).

These studies add to previous findings that indicate the importance of assessing the consequences of perivascular drug distribution and uptake when considering the translational potential of molecules for CED. The precise perivascular location of drugs delivered to the brain by CED varies according to the physicochemical characteristics of the infusate: interstitial fluid and low molecular weight solutes drain from the interstitial spaces of the brain along the basement membranes of capillaries and arteries (82), whereas infusates of particles with diameters exceeding 20 nm accumulate in the potential space between the outer wall of arteries and the glia limitans of the surrounding brain (13).

While an understanding of the ultrastructural anatomy of the perivascular and interstitial spaces of the brain is clearly relevant to achieving effective CED, the macroscopic anatomy of the targeted brain structure and adjacent structures is also important. High-volume CED infusions in a canine model of spontaneous glioma were associated with ventricular compression and leakage of infusate into the ventricles—events that could have serious adverse effects in a clinical setting (84).

EXPERIENCE IN NEURO-ONCOLOGY

The majority of preclinical and clinical CED studies have focused on the treatment of high-grade glioma. CED has a number of potential advantages for application in neuro-oncology, where inadequate penetration of the BBB is implicated in the poor response to systemically administered chemotherapies (91). Although increasing the concentration of a systemically administered chemotherapy can result in improved penetration of the BBB, this strategy risks intolerable side effects and systemic toxicity.

CED trials in neuro-oncology have used a wide range of therapies including conventional chemotherapies (paclitaxel, topotecan, nimustine), targeted toxins (IL13-PE38QRR, TP-38, PRX321), oligonucleotides and TGF-β2 inhibitors (10, 11, 14, 42, 45, 65, 70). The results of these clinical trials, with a few notable exceptions, have been somewhat disappointing—a situation largely attributed to poor drug distribution and reflux, resulting in off-target side effects and subtherapeutic drug concentrations within

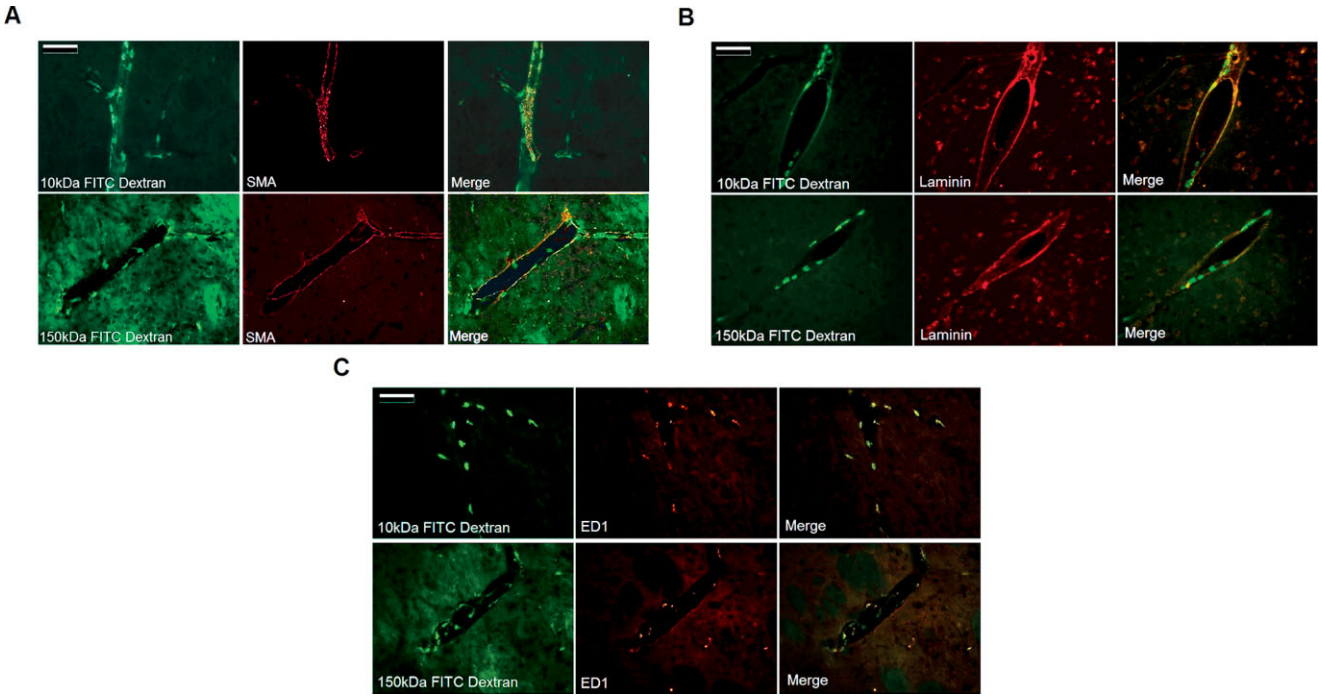

Figure 3. *Intrastriatal CED of a model solute (FITC dextran, green) in rat brain resulted in widespread perivascular distribution irrespective of molecular weight.* Colocalization with smooth muscle (SMA, red, **A**) in the walls of arteries and arterioles, laminin (red, **B**) and ED1-positive perivascular cells (red, **C**) was detectable at very early time points after infusion (scale bar = 100 μm). Reprinted from Barua *et al* (4). Copyright held by the authors (2012).

the tumor target (42, 45, 58, 74). A major problem in many of these early clinical studies was an inability to visualize the distribution of the infused therapy in relation to the tumor target or along the catheter track. A number of studies also reported unacceptable device-related adverse events (10).

The lessons from these studies are clear—for CED to be effective in neuro-oncology, it is necessary to combine optimized catheter technology with an infusate that has physicochemical characteristics suitable for CED and is delivered by an effective infusion regime, to achieve reflux-free infusions restricted to the desired structural target.

EXPERIENCE IN PD

A number of clinical studies have been undertaken with the aim of delivering GDNF directly to the posterodorsal putamen, which is known to be the site of greatest dopaminergic neuronal depletion in PD. Gill *et al* (22) enrolled five patients with symptoms poorly controlled by medical therapy into the first open-label study of continuous intraputaminal delivery of GDNF via microcatheters attached to a subcutaneous infusion pump in the anterior abdominal wall. All five patients demonstrated improvement in clinical and 18F-dopa positron emission tomography (PET) imaging parameters. Patients entered into a 12-month extension study showed sustained improvement without serious adverse effects (60). One patient receiving unilateral infusion of GDNF died of causes unrelated to the study, and post-mortem examination confirmed that infusion of GDNF into the posterodorsal putamen resulted in a marked increase in tyrosine hydroxylase-positive nerve fibers in the putamen and an increase in growth-associated protein 43 in the ipsilateral substantia nigra (47).

After a second successful open-label study by Slevin *et al* (79) enrolling 10 patients, a multicenter randomized controlled trial was commenced in the UK and United States. Thirty-four patients were randomized to receive either bilateral infusions of GDNF into the putamen or placebo (43). After 6 months, patients receiving GDNF had failed to demonstrate sufficient clinical improvement to achieve statistical significance despite improvements in PET imaging parameters. The disappointing results of this randomized study led to withdrawal of GDNF and cessation of clinical trials.

Technical variations in catheter design and drug delivery were suspected to have contributed to the failure of the multicenter trial following the success of the open-label studies. To investigate this hypothesis, Salvatore *et al* (71) analyzed the distribution of ^{125}I-radiolabelled GDNF in the putamen of nonhuman primates after infusion using the same delivery system as in the multicenter study. Radiographic analysis of GDNF distribution within the putamen revealed significant variability, with most of the GDNF restricted to the immediate vicinity of the catheter tip. The authors concluded that when translated to the human putamen, the bioavailability of GDNF would have been limited to 2–9% of the putaminal volume.

Significant research has subsequently been dedicated to applying CED to the treatment of PD with the aim of overcoming poor drug distribution. Intraputaminal CED of adeno-associated virus

serotype 2 (AAV2) expressing human aromatic L-amino acid decarboxylase (hAADC) was successfully performed in 10 patients with PD (85), and a phase II study is currently underway. A randomized double-blind phase II study of CED of GDNF using an intermittent infusion paradigm has also recently commenced, which has been designed to address the pitfalls of prior studies.

POTENTIAL IN ALZHEIMER'S DISEASE

In contrast to PD and high-grade glioma, there is no easily identifiable surgical target for CED in AD. Neuronal damage and degeneration in multiple brain regions including the medial temporal lobe and associated memory circuits, basal forebrain and cerebral cortex have been implicated in the progression of cognitive decline. As such, it is likely that for a therapeutic agent delivered intraparenchymally to be clinically effective in AD, it must be administered to multiple brain regions.

The primary abnormality in AD is thought to be the abnormal accumulation of Aβ within the brain. The main pathways for Aβ removal are enzymatic degradation, microglial uptake and degradation, receptor-mediated transport across the cerebrovascular endothelium, and bulk flow within the interstitial fluid through the perivascular extracellular matrix. Recent interest in amyloid-degrading enzymes as potential therapeutic agents has raised their profile in Alzheimer's research (53). To investigate the potential of using CED to promote Aβ degradation and clearance, we recently undertook preclinical studies of CED of neprilysin (NEP).

Convection-enhanced delivery of NEP

NEP, the prototypic Aβ-degrading metalloendopeptidase, is one of the most efficient of a range of thiorphan- and phosphoramidon-sensitive endopeptidases in degrading Aβ *in vitro* (53, 78). NEP was initially identified as a regulator of Aβ level when infusion of thiorphan—a NEP inhibitor—into rat striatum elevated the level of exogenously administered radiolabelled Aβ (32). Genetic ablation of the *NEP* gene in hAPP mice confirmed the importance of NEP in preventing Aβ accumulation: endogenous Aβ increased, and clearance of exogenously administered Aβ was impaired although not completely inhibited (33).

Inactivation of *NEP* in hAPP mice not only increased Aβ, including oligomeric Aβ (29), causing plaque-like deposits to form in the brain, but also impaired synaptic plasticity, caused behavioral and cognitive abnormalities (29, 51) and cerebral amyloid angiopathy (21). The severity of CAA was greater in $NEP^{-/-}$ than $NEP^{+/-}$ mice (21). Infusion of thiorphan in rats was also associated with impairment of cognitive performance (57, 96).

Overexpression of human NEP (approximately eightfold increase) in hAPP (Swe/Ind) transgenic mice markedly reduced cerebral Aβ, largely preventing plaque formation, and significantly improved life expectancy (44, 63). The combined data from *in vitro* and *in vivo* studies suggest that increasing the levels of NEP in the brain may have therapeutic potential for the treatment of AD.

Injection of lentivirus or adenovirus encoding human *NEP* into the hippocampus of hAPP mice reduced Aβ load and significantly improved performance in memory tasks (34, 52). However, this approach is associated with systemic and local immune responses, which can neutralize the therapeutic effects (48). Long-term gene transfer of human NEP in hAPP mice reduced intracellular and extracellular Aβ and improved behavior and memory (20, 80). Mice also showed evidence of reduced oxidative stress and inflammation (20) and less synaptic and dendritic damage (80).

Although viral vector-mediated *NEP* gene delivery has proven effective in transgenic mouse models, there are significant ethical and practical barriers to the translation of this approach to clinical trials. Many of these problems might be overcome by delivery of NEP directly to the brain by CED. In our studies, intrastriatal CED of human recombinant NEP in adult Wistar rats resulted in widespread interstitial and perivascular distribution (Figure 4), a 20-fold increase in NEP protein level, a corresponding increase in NEP enzyme activity, and no evidence of toxicity. Furthermore, in normal-aged rats, CED of NEP produced a significant reduction in endogenous Aβ40 within 24 h of a single infusion.

By using relatively high flow rates (2.5 μL/minute), it was possible to distribute NEP throughout a large volume of the striatal interstitium. The use of high flow rates is of importance for clinical translation, and with a volume of infusion (Vi) to volume of distribution (Vd) ratio of 4.6, NEP has significant potential for application to the clinical setting.

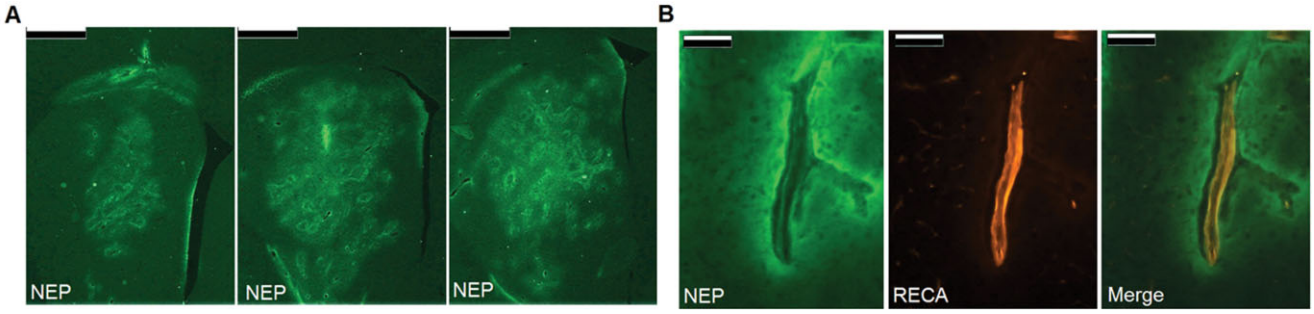

Figure 4. A. Intrastriatal CED of NEP (green) resulted in widespread interstitial distribution through large volumes of the striatum (scale bar = 1 mm). **B.** CED was also associated with perivascular distribution with accumulation of NEP external to the endothelium marked with RECA (red, scale bar = 100 μm). Reprinted from Barua *et al* (5). Copyright (2012), with permission from IOS Press.

The gray matter volume of the basal forebrain cholinergic system (including the nucleus basalis of Meynert) has been estimated at approximately 350 mm^3 in patients with mild AD (26). With a single CED catheter targeted to the human basal forebrain, it may be possible to distribute NEP throughout this structure with a 30-minute infusion time at a flow rate of 2.5 μL/minute, based on a Vi : Vd ratio of 4.6. This extrapolation is based on the assumption that the Vi : Vd ratio demonstrated in rat striatum (5) is directly translatable to the human basal forebrain.

However, the clearance of NEP from the brain following CED was found to be unexpectedly rapid, with levels returning to baseline within 24 h of infusion. The short half-life of exogenously administered NEP introduces the requirement for intermittent CED if this approach is to be effective. Although the short half-life might be thought to limit the therapeutic potential of this Aβ-degrading strategy, significant advantages are conferred by the rapid clearance from the brain. The rapidity of clearance allows close and dynamic control of dosing, and immediate cessation of treatment in the event of unforeseen adverse effects—such fine control is not possible with viral vector-mediated gene therapy. And although the short half-life of NEP imposes the need for repeated drug administration, advances in CED technology are already meeting this challenge. We recently described the use of an implantable CED catheter and transcutaneous port system, which facilitate chronic intermittent drug delivery (7, 8).

Therapeutic strategies applicable to CED

CED is potentially applicable to a number of AD therapies in addition to enhancing Aβ degradation and clearance. Nerve growth factor (NGF) is important for the survival and maintenance of the cholinergic basal forebrain and hippocampal cells, and is produced in the cerebral cortex and hippocampus, which are targets of these projection neurons. See Allen *et al* (3) for an in-depth review of the therapeutic potential of NGF in AD. The targeted intracerebral injection of NGF protein and cell-based gene therapies were previously trialed as neurorestorative therapies in AD (83, 87). However, the therapeutic potential of both of these strategies may be hampered by limited drug distribution, a problem that could be overcome by CED of neurotrophin-based treatments in AD.

The application of nanotechnology to CED also offers further opportunities for the treatment of AD. Nanoparticles are formulations of synthetic chemical components that self-assemble into particles of less than 1000 nm in diameter. Their size makes them a potential vehicle for CED, as the effective pore size of the extracellular matrix is on a nanometer scale. By altering nanoparticle formulations, it may be possible to enhance the distribution characteristics of infusates, to improve or inhibit cellular uptake and to facilitate slow release of therapeutic agents (49, 50, 62).

There is also significant interest in developing viral vector-mediated gene therapies for CED (12, 19). In addition to enhancing expression of a desired transgene, CED of small-interfering RNAs (siRNAs) could offer a means of knocking down genes encoding enzymes involved in Aβ production, such as β- and γ-secretases (61, 81).

Recent preclinical studies have demonstrated the potential of combining CED with axonal transport for delivering viral vector-mediated gene therapies to specific regions of the cerebral cortex. This has potential in a wide range of neurological diseases, including AD and several other forms of dementia. Convection-enhanced delivery of adeno-associated virus (AAV)-based vectors to the thalamus was shown to result in transgene expression in widespread cortical areas as a consequence of both anterograde and retrograde transport of AAV vectors (36).

CLINICAL TRANSLATION—REAL-TIME IMAGING

The experience gained from clinical trials in neuro-oncology and PD is strong evidence of the critical importance of understanding and controlling drug distribution within the desired target. Much research interest has focused on real-time magnetic resonance tracking of infusate distribution. Co-infusion of gadolinium and gadolinium surrogates, such as encapsulating liposomes, facilitates T1-weighted tracking of distribution (24, 70, 75). However, this approach assumes that the distribution of contrast agent is equivalent to that of the therapeutic agent. Although gadolinium-based contrast agents are generally considered to be stable complexes, it seems prudent to determine whether they alter the therapeutic effect of co-infused drugs as exchange reactions with metal ions are known to occur at physiological conditions (77). T2-weighted MRI signal change has also been used as a surrogate marker of infusate distribution (5, 68). Yet, it seems likely that T2-weighted imaging significantly underestimates the volume of distribution of the infused therapy (35).

The use of T2 imaging for real-time tracking may be of more practical use in patients without preexisting T2 abnormalities on MRI. Co-infusion of radiolabelled infusates or infusion of radiolabelled therapeutic agents are alternative strategies that have been used to good effect in clinical trials, particularly in neuro-oncology. ^{123}I-labelled human serum albumin was co-infused with cintredekin besudotox, and single-photon emission computerized tomography (SPECT) matched with co-registered MR images (73). In a second study, ^{123}I-labelled therapeutic antitenascin monoclonal antibodies were administered by CED in patients with glioblastoma and the volume of distribution was analyzed by SPECT (72). However, it has proven difficult to correlate T2 signal change induced by CED in patients with preexisting T2 hyperintensities with volumes of distribution on SPECT (73).

Despite these flaws, real-time tracking of infusions is fundamentally important for ensuring successful clinical trials by providing the investigator with confidence that the therapy is reaching (and limited to) the desired target. However, interpretation of the data obtained by MRI should ideally be based on information from combined neuropathological, biochemical and imaging studies using the same infusates and CED equipment in animal models as in clinical trials.

CONCLUSIONS

CED has the potential to improve the treatment of a wide range of neurological conditions. The theoretical advantages of CED are multiple and include bypass of the BBB, limitation of systemic side effects, delivery of therapeutic drug concentrations and distribution through clinically relevant brain volumes. However, most preclinical and clinical CED research to date has focused on drug

delivery for diseases characterized by localized pathology, such as brain tumors, or diseases in which a localized surgical target can be identified, such as PD.

The widespread pathology associated with neurodegenerative disease states such as AD adds an additional layer of complexity, as it is likely that an effective treatment for AD would require delivery to multiple brain regions including the basal forebrain, medial temporal lobe and cerebral cortex. The facility to distribute a drug through very large volumes of brain tissue depends on both the physicochemical characteristics of the infused therapy and the technology used to deliver it.

The interstitial distribution of liposomal drugs delivered by CED is dependent on the infused agent having low tissue affinity (49). Further investigation is required to determine whether the most widely distributed soluble agents are low molecular weight hydrophilic and/or anionic compounds (69). Further study is also required to determine whether infused agents with low tissue affinity are likely to be rapidly cleared from the brain, as suggested by the CED of NEP. This possibility introduces the requirement for either repeated intermittent drug infusions or, in the case of proteins, gene therapy.

The design and development of a chronically implantable catheter and transcutaneous bone-anchored port makes it now feasible to perform intermittent CED via multiple catheters (7). This technology is currently being used for the treatment of recurrent glioblastoma and could be applied to a CED trial in AD.

Effective clinical translation of CED will be dependent on the adoption of suitable catheter technology and implantation methods, used in combination with therapeutic agents that have appropriate physicochemical properties. Extensive preclinical studies correlating infusate distribution with neuropathological and neuroradiological findings are also required to maximize the chances of success in a clinical setting.

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DISCLOSURES

NB is a consultant advisor to Renishaw Plc, a manufacturer of drug delivery catheter systems. SG is Renishaw's clinical director.

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