Convection-enhanced delivery to the central nervous system

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Convection-enhanced delivery (CED) is a bulk flow–driven process. Its properties permit direct, homogeneous, targeted perfusion of CNS regions with putative therapeutics while bypassing the blood-brain barrier. Development of surrogate imaging tracers that are co-infused during drug delivery now permit accurate, noninvasive real-time tracking of convective infusate flow in nervous system tissues. The potential advantages of CED in the CNS over other currently available drug delivery techniques, including systemic delivery, intrathecal and/or intraventricular distribution, and polymer implantation, have led to its application in research studies and clinical trials. The authors review the biophysical principles of convective flow and the technology, properties, and clinical applications of convective delivery in the CNS.

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KEY WORDS convection-enhanced delivery; drug delivery; central nervous system; technique; bulk flow

Biophysical Principles of Convective Flow

Within the extracellular space of the CNS, fluids and agents move either by diffusion or by bulk flow. Diffusive flux (J) depends on the concentration gradient (VC, where V is the gradient operator), as stated by Fick’s law, J = –DVC, where tissue diffusivity (D) is highly dependent on the molecular weight of the molecule. Unfortunately, effective diffusion times are long for macromolecular therapeutic agents, and transport depends on large concentration gradients, often requiring unacceptably high

ABBREVIATIONS BBB = blood-brain barrier; CED = convection-enhanced delivery.


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concentrations near the drug source. As a result, extensive
distribution by diffusion is not possible for macromole-
cular therapeutic agents of interest for most disorders, and
practically, diffusive penetration in brain tissue is gener-
ally limited to a few millimeters.57

Bulk flow is extracellular fluid flow that can exist un-
der either normal or abnormal (for example, edema)7 con-
ditions. Within the CNS, these flows can be modeled
by treating tissue as a hydrated porous medium consist-
ing of fluid and solid phases, in which the fluid phase is
the interconnected interstitial space and the solid phase
is the aggregation of cellular, vascular, and extracellular
matrix constituents. Bulk flow is driven by fluid pressure
gradients that exist within tissues and can be modeled by
Darcy’s law, which asserts that the velocity of fluid (v) is
directly related to the tissue pressure gradient (∇p): v =
−K∇p, where hydraulic conductivity (K) is a measure of
flow conductance. Compared with diffusion, bulk flows
are largely independent of molecular weight.

In CED, a cannula is discretely introduced directly into
the nervous system interstitial spaces with its tip at the
target site. Controlled infusions induce bulk flows, which
distribute infusate over large volumes within the extracel-
ular space and are capable of achieving multicentimeter
depths of penetration. During CED, transport to sur-
rounding tissue depends on bulk flow, as well as diffusion
and clearance loss due to permeation and reaction. The
balance between these sources and sinks determines the
overall penetration distance. Theories for CED at a con-
stant infusion rate into homogeneous brain tissues provide
the simplest possible expression to describe concentration
profiles and penetration distances. In this model, inter-
stitial bulk velocity (v) varies radially around a spherical
cannula source and is solved using the continuity equa-
tion (differential mass balance of water in brain tissue) and
Darcy’s law: v(r) = q/(4πr²), where q is the infusion flow
rate and r is the radius from the cannula tip. More complex
analytical solutions for infusion from a cannula source
have also been developed that account for water uptake
in tissue30 and tissue swelling with pressurization.5,17,85

Tissue transport of the infused species is described by
a differential mass balance relation governing tissue con-
centration as a function of space and time, which is for-
mulated to account for convection, diffusion, metabolism,
binding, and net transport across the microvasculature:
∂C/∂t = D∇²C − V(∇C/f) − kᵦC/f − P × s(C/f − Cₛ), where
kᵦ is the first-order metabolic rate constant in tissue (the
rate of degradation), f is the fluid volume fraction (poros-
ity), Cₛ is the plasma concentration of infused solute (usu-
ally 0), and P × s is the product of permeability coefficient
and surface area per volume of tissue that accounts for the
passive movement of infusate across vessels. When need-
ed, f can be replaced by another constant accounting for
weak binding of infusate species to tissue components.68
This equation is generally solved numerically.

Simulations for nonbinding 180-kD macromolecules
delivered at 3 μl/min from a spherical source into homo-
geous tissue are associated with radial penetrations of
1.5 cm in 12 hours with relatively flat and uniform profiles
(“square-shaped” concentration profile) that decline dra-
matically at the advancing front (Fig. 1).62,69 Initially, trans-
port is dominated by convection, and the advancing front
approximates a step function. With time, the steepness
and bluntness of the advancing front decreases because
of the superimposed contributions of diffusion and clear-
ance. After the cessation of infusion, further transport of
the drug will occur through tissue by continued convect-
ion (as long as a pressure gradient from the infused region
persists) and by diffusion until clearance mechanisms
clear the drug entirely from tissue. This phase should be
considered in any dose-response estimation.

Recently, Sarntinoront and colleagues100–102 devel-
opened an integrated finite element formalism model that
can be used to optimize the distribution of substance
P–associated protein toxin to the spinal cord for chronic
neuropathic pain treatment. This model accounts for the
anisotropic transport in the spinal cord, the anatomical
boundaries throughout the spinal cord substance, as well
as substance P–associated protein toxin binding/uptake,
metabolism, and dose response. Further, groups have used
computational analyses based on diffusion tensor imaging
(an MRI technique that measures the restricted diffusion
of water in nervous system tissues and measures axonal
alignment) that account for preferential fluid flow and dif-
fusion transport directions, which can vary in the extracel-
ular spaces within complex nervous system anatomical
structures.39,40,55,89,101

**Convective Delivery Technology**

**Infusion Apparatus**

Direct transmission of a small controlled pressure dif-
ferential is required for the steady flow of infusate into the
extracellular CNS spaces. Constant and reliable pressure
transmission during infusion demands a noncompliant
infusion system. To minimize compliance in the infusion
apparatus and reduce infusate binding, infusate reservoirs,
tubing, and cannula are derived from noncompliant mate-
rials, including silicate, hardened plastic, and metals. The

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**FIG. 1.** Convection-enhanced delivery interstitial concentration profiles for a 180-kD macromolecule in nonbinding brain tissue. Simulations are for varying times during infusion at 3 μl/min and include drug degrada-
tion (33 hours characteristic time for degradation), cannula geometry (32 gauge), and tissue and vascular transport properties as listed in Morrison, 2001.
minimization or elimination of system compliance allows precise delivery of the infusate in either continuous or bolus convective flow patterns. Large-animal (primate) data indicate that that convective distribution of the infusate in the CNS is similar, feasible, and safe using either flow pattern if a noncompliant system is utilized.71

**Infusion Cannula**

Mathematical modeling, preclinical animal data, and clinical data indicate that the infusion cannula design affects the success of convective delivery to the CNS by reducing infusate leakback around the cannula at higher infusion rates and by eliminating intraparenchymal air entrainment (associated with catheters with an inner stylet) during insertion.14,41,68,90,114 Specifically, the minimization of cannula tip diameter, which reduces tissue expansion, is a way to minimize leakback during infusion and has been demonstrated by mathematical modeling and animal data.68 Further, avoiding entrainment of intraparenchymal air that occurs with malleable infusion catheters upon removal of the rigid inner stylet needed for accurate placement of the tip is necessary to avoid preferential distribution in the tissue air pocket. These critical cannula properties have been achieved through the development of inner infusate cannula-outer guide cannula combinations.22,31,62 hollow fiber tubes,77,78 as well as step-design cannulae.41,54

**Properties of Convective Delivery**

**Bypassing the BBB**

Because putative therapeutics are perfused directly into the CNS using CED, the delivery of infusate bypasses the BBB. Further, the compounds that do not cross the BBB are the ideal agents to distribute via CED. Therapeutic compounds that do not readily penetrate the BBB from the systemic circulation, when delivered by convection, remain sequestered on the abluminal side of the BBB within the perfused parenchyma for prolonged periods until they are metabolized and cleared from the interstitial spaces.7,15,21,60,69 Consequently, large-molecular-weight (>400 D) and/or hydrophilic compounds are best for CED. Thera-

**Targeted Delivery**

Because infusate is distributed directly into site-specific regions of the CNS from an infusion cannula, the distribution of therapeutic agents is targeted. Previous studies have demonstrated that deep brain nuclear targets can be selectively perfused with small- and large-molecular-weight compounds (Fig. 2).32,54,57 Moreover, large-animal data indicate retrograde or anterograde transport of delivered therapeutics, including proteins, and transgene expression of products delivered by viral capsids or bacteriophage can be distributed from the perfused CNS region to other distant nonperfused regions via interconnecting white matter tracts in a highly predictable manner.30,38,42,54 These features of CED in the CNS permit manipulation of precisely targeted regions or regulation of broader anatomical regions via upstream or downstream effects of infusate delivery.

**Homogeneous Distribution**

Unlike diffusion-driven distribution, which results in limited tissue penetration from the diffusive surface (1 to 2 mm) and a steep drop-off in concentration over that distance (250- to 1000-fold decrease)6,105 bulk flow of the infusate during CED permits homogeneous distribution of infusate throughout a perfused tissue region. Autoradiographic analysis of infusate distribution in a large-animal brain, brainstem, spinal cord, and peripheral nerve demonstrates the homogeneity of convective delivery.7,58,63,72 Analysis of the distribution of radiolabeled compounds in animals euthanized immediately after completing a brief infusion via CED demonstrates a homogeneous “square-shaped” distribution pattern in gray and white matter consistent with a uniform high concentration of infusate over a perfused CNS region. Thus, biological and pharmacological effects that depend on the concentration of a

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**FIG. 2.** Gliarial-derived neurotrophic factor (GDNF) protein distribution after thalamic infusion of adeno-associated virus Type 2 serotype (AAV2)-GDNF. Immunohistochemical staining demonstrates GDNF expression in the prefrontal cortex on the same side as thalamic infusion of AAV2-GDNF (A). Cortical neurons positive for GDNF were found in the prefrontal cortex (Areas 9 and 10, B and C). Premotor cortex, frontal eye field, Broca’s area, cingulate cortex neurons (D–G), as well as neurons of laminae V and VI in prefrontal cortex (E and F) and frontal eye fields (H and I) were GDNF-positive. The GDNF-positive neurons were evident above the pyramidal neurons in cortical layers. GDNF-positive neurons were found at the infusion site in the thalamus (J), as well as in the cortical neurons in the somatosensory and motor cortex. Laminae V and VI of the somatosensory cortex neurons were also GDNF-positive (K and L). AP = anterior-posterior distance (in mm) from the bregma. Numbers indicate different cortical areas referenced in the text. Bar = 5 mm (A, D, G, and J); 500 μm (B, E, H, and K); 100 μm (C, F, I, and L). Reproduced from Kells et al.: Proc Natl Acad Sci U S A 106:2047–2411, 2009.
anisotropic and isotropic Flow Patterns

Regional disorders. This property permits treatment of large systems can be perfused with drug in a relative-throughout the nervous system, large regions of nervous flow to move small- and large-molecular-weight infusate over a wide range of Compounds

Clinically Relevant Distribution

Small or large clinically relevant volumes of perfusion are possible with convective delivery in the CNS. While convective perfusion of nuclear targets is feasible during an acute infusion (over minutes to hours), protracted infusion can be used to completely perfuse significant regions of a cerebral hemisphere, the brainstem, and the spinal cord (Fig. 3). A significant limitation of other conventional delivery techniques is the inability to distribute drug in high concentrations in a targeted manner over large regions of the CNS. Because CED relies on bulk flow to move small- and large-molecular-weight infusate throughout the nervous system, large regions of nervous system structures can be perfused with drug in a relative-

Anisotropic and Isotropic Flow Patterns

While distribution of infusate in gray matter is isotropic (approximating a spherical distribution pattern around the tip of the infusion cannula), convective distribution of infusate into white matter is anisotropic and occurs preferentially along parallel white matter tracts. The preferential infusate flow along white matter tracts can be exploited to fill large regions of white matter from a single infusion point source. Specifically, infusion in the cerebral white matter tracts (for example, corona radiata) can be used to rapidly fill regions of the cerebral hemisphere and immediately subjacent cortical gray matter from a single infusion cannula. Similarly, convective infusion into the parallel lateral corticospinal tracts results in perfusion over several segments of the spinal cord.

Effects of Anatomical Boundaries

Convective tissue perfusion efficiency near pial and ependymal surfaces can be adversely affected once the leading edge of infusion meets these anatomical surfaces. Primate and clinical infusion data demonstrate that once the leading edge of a convective infusion encounters a pial or ependymal surface, the tissue distribution volume to infusion volume ratios decline as leakage of the infusate (small and large molecular weight) into the CSF of the cistern or ventricle occurs. Once infusate begins to cross these surfaces, a portion of the total infusate is lost into the CSF and is not distributed to tissue, reducing the distribution. The distribution volume will continue to decline compared with the distribution that would otherwise occur as a larger portion of the infusion volume encounters a pial or ependymal surface and a larger fraction of the total infusate is lost to the CSF space.

Application Over a Wide Range of Compounds

Convection-enhanced delivery permits the distribution of compounds with a wide range of molecular weights in the CNS. Convective delivery has been used to deliver small compounds (< 1 kD), including chemotherapeutic agents, amino acids, and low-molecular-weight imaging tracers. Alternatively, CED has been used to distribute proteins, virus and/or virus-sized particles, liposomes, and nanoparticles. While small- and most large-molecular-weight compounds will distribute by convective flow in a similar manner, viruses, virus-sized particles, and nanoparticles have restricted flow (tissue distribution volume to infusion volume ratio of 2:1 to 3:1) This reduction in delivery efficiency is attributed to limits in the size of the extracellular space in the CNS, which has been estimated to be on the order of 100 nm and to certain features of the infused nanoparticle.

Imaging of Convective Distribution

Use of co-infused surrogate imaging tracers to track convective delivery in real time provides an opportunity to increase the effectiveness and safety of CED, to permit reliable assessment of therapeutic efficacy (by confirming successful delivery and distribution), and to better
define the properties of CED in the CNS. Preclinical data demonstrate that CT and MRI tracers can be co-infused to accurately assess convective infusate distribution (Fig. 3).3,16,22,25,27,29,59,76,106 Because CED relies on bulk flow and because most large- and many small-molecular-weight compounds distribute at a similar rate during the typical time course of CED, surrogate tracers that differ substantially in size from the putative therapeutic can often be used to track drug distribution over infusion volumes necessary to treat many neurological disorders.

There are small-molecular-weight (< 1 kD) contrast agents for CT and MRI that are approved for clinical use and that can be used as surrogate tracers to track distribution during CED. Real-time imaging of CED is possible and has been used safely in animal and clinical trials to track small- and large-molecular-weight therapeutic compounds.3,18,59,110 While the small-molecule surrogate imaging tracers iopamidol and Gd-DTPA will accurately track large therapeutic compounds over infusate volumes sufficient to perfuse discrete disease-specific regions, the use of these surrogate tracers for tracking macromolecular distribution over large volumes and with prolonged infusion times will not accurately reflect the distribution of the drug, because of the tracer’s long-term clearance by microvascular efflux and the long-term diffusional broadening associated with its low molecular weight.

In the case of the CT contrast agent iopamidol, experiments have shown that this small-molecule surrogate tracer accurately provides estimates of dextran (70 kD) distribution volumes (that is, less than 20% difference between imaged and actual distribution volumes) provided that infusion rates (qi) are not too slow for a given total infusion volume (Vi).22 For these specific compounds, modeling has shown that for a desired Vi (in μL), qi (in μL/min) must be chosen so that qi ≥ Vi / 600. From such empirical relationships, it is likely that many neurological disorders can be investigated with the expectation that the infusate volume required would be accurately tracked using a small-molecular-weight contrast agent—provided that the therapeutic compound, large or small, is negligibly reactive and confined to the extracellular space.

Because CED relies on infusate delivery into the interstitial spaces of the CNS, T2- and diffusion-weighted real-time MRI has been used to track drug distribution.38,91,98 Qualitative T2- and diffusion-weighted changes have been shown surrounding the infusion cannulae and areas of infusate distribution in these studies. Nevertheless, when qualitative autoradiographic assessment of the accuracy of the T2- and diffusion-weighted sequences was performed,35 it was revealed that these MRI sequences significantly underestimated the distribution of both small and large molecules. Specifically, these imaging techniques underestimated the volume of distribution of small- (sucrose) and large- (albumin) molecular-weight distribution using CED by 49%–60%.35

Safety of Convective Delivery

Increasing the fluid content of the interstitial space leads to edema in the perfused region. Previous studies have shown, however, that even when 180 μl was infused into a rat brain over 2 hours (a volume sufficient to fill more than an entire rat hemisphere), intracranial pressure never rose above 8 mm Hg.9 While brain edema in eloquent areas can cause transient neurological symptoms, the deficits are reversible if intracranial pressure is maintained in the normal range and the vascular supply to the brain is not impaired.50 Since intratissue pressure remains in the normal range with CED, the infusion of large volumes (even with near hemisphere filling) has no effect on blood flow to the perfused regions. This explains why permanent neurological injury has not occurred as a result of large-volume infusions. These clinical findings are also confirmed by histological studies showing no tissue damage in infused regions after CED.

It is possible that convective delivery could cause expansion of the interstitial space and symptomatic edema infusion at high rates, prolonged infusion (for example, chronic infusions), and infusion of very large volumes (for example, holohemispheric). The excess fluid, especially with rapid or high-volume infusions, in the region of a preexisting mass, such as a tumor, could induce herniation with its attendant serious effects. Despite these concerns, irreversible neurological deficits and significant intracranial pressure increases associated with convective delivery rarely occur in small animals, nonhuman primates, or humans (over 200-ml infusions into the brain in patients with brain tumors).49,81 If deficits occur, they rapidly reverse with the cessation of infusion and/or glucocorticoid administration.

Despite the well-defined safety of CED of therapeutics in the CNS, there have been reported cases of lasting or irreversible neurological changes in animal studies and human clinical trials.2,44,49,71 These neurological changes have been attributed to prolonged edema or effects of the drug on tumor (in tumor-specific trials and/or the putative therapeutic infused at doses in a potentially tissue toxic range). Lasting or irreversible neurological changes directly attributed to the convective infusion of substances in the CNS have not occurred over a range of infusate rates, including rates up to 10 μl/min.

Clearance of Solutes After CED

During the postinfusion phase, solute (particularly small molecules) continues to redistribute, both via natural bulk flow and diffusion. However, as a result of continuing local clearance of the infusate, diffusional expansion of the perfused region is limited for most agents.69 Further, because of the square-shaped distribution curve associated with most CED protocols, postinfusion diffusion is confined to the steep edge of the distribution, and this generally contributes negligible extension to the tissue penetration depth already achieved at the end of the infusion proper. Only in the case of small infusion volumes would such diffusion significantly increase the tissue distribution volume.

Clinical Application of Convective Delivery

Convective Delivery Paradigms

Targeted Therapeutics

A number of new targeted therapeutics have been developed to address a wide variety of neurological disor-
The properties of CED are being exploited to deliver these therapeutic agents to site-specific regions of the CNS to investigate a variety of disorders that are currently untreatable or cannot be addressed using other available CNS drug delivery methods. Ideal agents for delivery by convection include those that are pathology selective, have a targeted CNS region for application, are metabolized at rates that permit them to be therapeutic, and do not effectively cross the BBB. Therapeutic approaches can selectively lesion or augment diseased CNS cell populations, regulate abnormal metabolic disease pathways, transiently alleviate pathophysiology, and/or target tumor cells for selective destruction. Neurological disorders and agents that have been investigated using CED are described in Table 1.

**Physiological Manipulation**

The ability to transiently augment or suppress the activity of targeted components of diseased neuronal circuits by selectively delivering neuroactive compounds presents a new opportunity to derive deeper insight into disease pathophysiology. Specifically, the ability to directly correlate the effects of the physiological manipulation of diseased brain structures with clinical effects represents an opportunity for understanding mechanisms of disease, introducing new methods of diagnosis, developing new treatments, as well as introducing and using new therapeutic agents. There are immediate opportunities to better understand disorders that have site-specific pathophysiological features, including Parkinson’s disease, essential tremor, obesity, anorexia nervosa, epilepsy, and behavioral disorders.32,50,79

**Future of Real-Time Imaging to Clinical Treatment Paradigm**

Previously, CED using new putative therapeutic agents was clinically applied in isolated cases or Phase I/II trials (Table 1). The only CED Phase III trial performed to date involved the infusion of the glioma toxin interleukin-13 bound to *Pseudomonas* exotoxin in patients with glioblastoma multiforme.43 This treatment did not show a significant increase in patient survival compared with treatment with bis-chloroethylnitrosourea (BCNU)–impregnated Gliadel wafers. Because real-time imaging of co-infused surrogate MRI agents was not used routinely and drug distribution could not be accurately established, coverage of the targeted tissues was not confirmed. Moreover, in most of the clinical trials, the investigation has combined a new (experimental) therapeutic agent with CED, a new drug delivery approach. The advantages and limitations of convective delivery in various clinical circumstances, as well as the efficacy of various agents, are not known.43,45,49,50,96,99,107,115 These circumstances underscore the need for real-time imaging of drug distribution, or surrogates of drug distribution, during CED in clinical studies and/or applications to verify targeting.

With improved CED procedures and infusion systems, emerging clinical data from real-time imaging has demonstrated that CED can treat clinically relevant regions and volumes in a targeted manner. Further, these early clinical data underscore the properties described in preclinical studies, enhance safety by permitting controlled distribution, and give direct insight into therapeutic efficacy. Moreover, data from real-time imaging of convective delivery in the CNS provide understanding of the properties of CED in various clinical circumstances. Specifically, critical information about the optimal infusion rate, effect of pial/epidymal surfaces, effect of previous surgery, vasoergic edema (when present), and preferred pathways of infusate flow can be derived from these studies.

**Limitations of CED**

While there are a number of advantages of CED in distributing therapeutic compounds to the CNS, there are also potential limitations. First, because CED requires cannula placement, it is more invasive than systemic delivery techniques. Second, drugs that easily cross the BBB will probably not be good drugs to deliver via CED, as they can readily leak through the CNS vasculature and into the systemic circulation. Third, therapeutics that are rapidly metabolized or taken up by CNS cellular components may limit the spread of infusate. Finally, improved targeting technologies that account for anatomical boundaries (that is, ependymal surfaces, pial surfaces, resection cavities, gray-white junctions) or pathological structural changes (that is, vasoergic edema or necrotic areas) will alter infusate flow and distribution and require longer infusion or multiple cannula placements to achieve therapeutic infusate coverage.

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**TABLE 1. Convective delivery for the treatment of neurological disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Therapeutic Agent</th>
<th>References</th>
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<td>Neuronal ceroid lipofuscinosis</td>
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AADC = aromatic L-amino acid decarboxylase; AAV = adeno-associated virus; CLN2 = neuronal ceroid lipofuscinoses; CNTF = ciliary neurotrophic factor; GDNF = glial-derived neurotrophic factor; GAD = glutamic acid decarboxylase.
Convective delivery

Predictive Modeling for Clinical Application

As the biomechanical principles of CED are better understood and confirmed via real-time imaging under a variety of pathological conditions, defined and accurate preclinical predictive modeling based on imaging should be feasible across a wide spectrum of neurological disease states. The ability to accurately predict optimal cannula placement and the capability to precisely anticipate infuse distribution based on preinfusion CT and MRI planning will be important for clinical trial development.

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Conception and design: Lonser, Sarntinoranont, Oldfield. Acquisition of data: all authors. Analysis and interpretation of data: Sarntinoranont, Morrison, Oldfield. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lonser. Administrative/technical/material support: Lonser.

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