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Review Article

Transnasal drug delivery to the brain: circumventing barriers for brain tumor patients

Eric T Wong, Edwin Lok

Brown University Health Cancer Institute and Rhode Island Hospital, Providence, Rhode Island, USA

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Abstract: The transnasal route is a novel mode of drug delivery into the brain. It has several advantages of circumventing systemic first-pass metabolism that attenuates bioavailability and bypassing the blood brain barrier that excludes multiple categories of drugs or biologics. These include most compounds that have high molecular weight and low lipid solubility, bioactive neuropeptides, and monoclonal antibodies that have potential neurotherapeutic effects. In this review, we summarized how drugs and biologics can be delivered into the brain via (i) the olfactory/nasal lymphatic route, (ii) the epithelial or other supportive cells by receptor-mediated micropinocytosis for transcellular delivery, and (iii) transneuronal transport through the olfactory and trigeminal neurons. Dexamethasone and neuropeptide corticorelin acetate can be taken up by the lymphatic route, while larger molecular weight entities such as checkpoint inhibitors, bi-specific antibodies, and antibody-drug conjugates may require the slower transepithelial or transneuronal transport system. Tumor Treating Fields may increase the permeability of the tissue near the cribriform plate and therefore facilitate entry of these high-molecular-weight neurotherapeutics into the brain. For brain tumor patients, transnasal delivery holds promise for the delivery of drugs like dexamethasone, neuroactive peptide, and monoclonal antibodies for the treatment of malignancies in the brain while decreasing systemic toxicities.

Keywords: Transnasal delivery, blood brain barrier, first pass metabolism, drugs, biologics

Introduction

Transnasal drug delivery into the brain is a novel concept in neuro-oncology. This route of administration can circumvent systemic metabolism that attenuates bioavailability of potential neurotherapeutics and the blood brain barrier (BBB) that excludes bioactive neuropeptides, monoclonal antibodies, and a majority of compounds that have high molecular weight and low lipid solubility [1, 2]. Additionally, the BBB is a formidable obstacle for a multitude of anti-cancer drugs for brain tumor patients. However, it is not completely impervious and there are regions that are permeable for selective drugs. The circumventricular organs and the cribriform plate are potential sites that offer this opportunity. This review will address challenges associated with drug penetration into the central nervous system (CNS), anatomy of the nose-brain interface, pharmacokinetic and pharmacodynamic considerations, as well as specific examples of potential delivery of transnasal drugs or biologics in neuro-oncology.

Drug penetration into the central nervous system is suboptimal

First pass metabolism attenuates drug bioavailability after systemic absorption

First-pass metabolism refers to the process by which a drug is metabolized in the liver and other organs before it reaches the systemic circulation. This process is particularly problematic for oral delivery to the brain because it reduces the amount of active drug available in circulation and eventually to the targeted end organ. After a drug is ingested, it passes through the digestive system for absorption, followed by entry into the portal circulation. The drug in the portal system is then delivered to the liver, where it is metabolized into both active and inactive forms. This involves enzymatic breakdown by the cytochrome P450 enzymes

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together with other enzymes in the phase I and II metabolic pathways [1]. Phase I metabolic pathways are biochemical processes that convert lipophilic drugs into more polar molecules [1]. These reactions can involve oxidation, reduction, or hydrolysis by introducing functional groups such as -NH2 or -OH. Phase II metabolic pathways facilitate detoxification and elimination by conjugation reactions such as glucuronidation, sulfation, glutathione conjugation, amino acid conjugation, acetylation and methylation [1]. Attachment of an ionizing group makes the metabolite more water soluble and facilitates its excretion while decreasing pharmacological activity in the body. The extent to which a drug is metabolized during first pass can significantly reduce its bioavailability. In addition, this process can also be altered by food intake, as well as the patient's age, gender, and genetic background. Drugs susceptible to increased first-pass metabolism often require higher oral doses to achieve a therapeutic level or they can be administered via alternative routes that bypass the liver such as intravenous, sublingual, or transdermal application. Therefore, first pass metabolism is a major obstacle for effective oral drug delivery to the CNS.

The BBB obstacle

The BBB is another formidable obstacle for efficient delivery of drugs and biologics into the brain. It is not a physical, but a physiological, barrier comprised of endothelial cells, astrocytes and basal lamina [2, 3]. First, the tight junctions between endothelial cells exclude large molecular weight substances (i.e. drugs, proteins, and viruses) from entering the brain. Second, these endothelial cells are coupled with the end feet from astrocyte projections, which help to support the endothelial tight junctions. Lastly, these cells are surrounded by a layer of extracellular matrix, further enhancing the exclusionary function of the BBB. Together, all three components help protect the brain from chemical and infectious insults.

The BBB is not completely impenetrable. It does allow entry of molecules possessing certain characteristics by passive diffusion, particularly those with small molecular weight, high lipophilicity and positive charged. Log P is the water partitioning coefficient for octanol and it measures the relative proportion of a drug or chemical dissolved in the organic and aqueous phases [4]. In general, those having a log P index of >1 and a molecular weight of <300 grams/mole would readily penetrate the BBB. Since the endothelial cell surface is predominantly comprised of intense negatively charged proteoglycans due to the presence of sulfate groups on their side chains, positively charged molecules have a higher probability of crossing the BBB [5-8]. Larger molecules, peptides and antibodies may require a transporter for entry.

Transporter proteins can selectively carry essential molecules, such as glucose and amino acids, from the systemic circulation into the brain. Glut1 is a major transporter of glucose and carries it passively across a concentration gradient into the endothelial cells and neurons [9]. SGLT1 and SGLT2 are coupled to ATP that actively pump glucose into cells [10]. SGLT1 is more abundant than SGLT2 in cerebral endothelial cells. Together, Glut1, SLGT1 and SGLT2 maintain metabolic homeostasis in the brain. Another major type of transport is for amino acids, such as dopamine and glutamine. L-DOPA is a precursor to dopamine, and it is transported into the brain by large neutral amino acid transporters (LAT1) [11]. LAT1 also carries other amino acids like phenylalanine, tyrosine, and tryptophan [11]. Once L-DOPA crosses the BBB, it is taken up by dopaminergic neurons, where it is decarboxylated to form dopamine [12]. Dopamine regulates the permeability of cerebral vasculature, and it is also an essential neurotransmitter for motor, neurocognition and the reward pathways in the brain [12]. Furthermore, glutamine addiction enables tumor cells to fuel their cellular bioenergetics and metabolism by glutaminolysis from L-glutamine to α-ketoglutarate, pyruvate and lactate, while NADH and FADH2 generated in the tricarboxylic acid cycle provide electrons for ATP generation in the mitochondria [13]. Therefore, transporters for both metabolites and amino acids play an essential and basic role in the homeostatic functions of the CNS.

Efflux pumps are specialized transporters on the endothelial cells, such as P-glycoprotein and other multidrug-associated resistance proteins, that actively pump out certain molecules that manage to enter the endothelial cells [14,

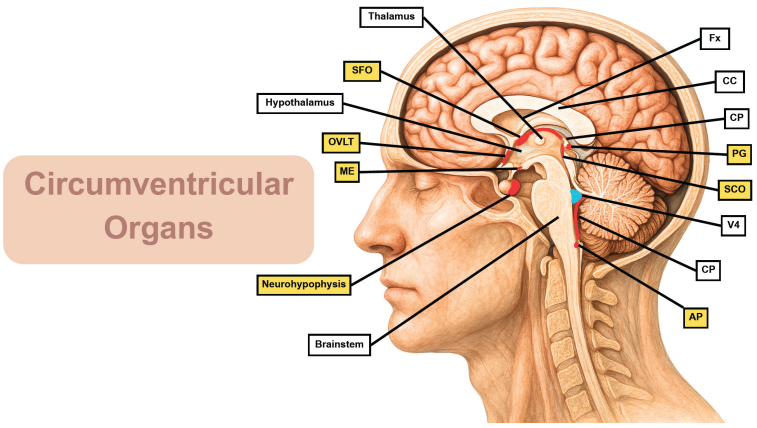

Figure 1. Circumventricular organs (AP, ME, Neurohypophysis, OVLT, PG, SCO and SFO). These intracranial structures lack a blood brain barrier and therefore there is a direct communication between the systemic circulation and the intracerebral space. AP, area postrema; CC, corpus callosum; CP, choroid plexus; Fx, fornix; ME, median eminence; OVLT, organum vasculosum at the lamina terminalis; PG, pineal gland; SCO, subcommissural organ; SFO, subfornical organ; V4, fourth ventricle.

15]. These efflux pumps recognize and expel foreign substances, including many drugs, before they can reach the brain. However, this function counteracts therapeutic drug entry into the brain. Although inhibitors of P-glycoproteins are available, they do not work very well and lack specificity for the brain.

Circumventricular organs without a BBB

The circumventricular organs are located at the periphery of the brain without a BBB (area postrema, median eminence, neurohypophysis, organum vasculosum at the lamina terminalis, pineal gland, subcommissural organ and subfornical organ) (**Figure 1**) [16]. They are thought to be sensors between the brain and the systemic circulation. They are also entry points for bacteria and viruses, as well as smaller size neuroactive peptides and hormones. Neurohypophysis and median eminence are two circumventricular organs closest to the nasal epithelium and cribriform plate. Surprisingly little is known about the microanatomical structure and makeup of the cortical bone next to the sphenoid sinus and the sella turcica. This is important because microvascular channels with diameters of 10-20 mm were found in cortical bones of the calvarium in mice and humans [17]. These channels allow an easier passage of immune cells from adjacent bone marrow into the subarachnoid space and the meninges. Therefore, if there are microvascular channels passing through the sphenoid bone and the sella turcica surrounding the nasal cavity, they could potentially serve as a conduit not only for entry of drugs and biologics applied into the nasal cavity but also activated immune cells as in cellular immunotherapies.

Infection, non-infectious inflammation, and neoplasm within the sphenoid sinus can spread into the CNS. The most dreaded form of rhinonasal infection is from fungal organisms such as Aspergillus or Mucormycetes [18]. These fungi can invade into adjacent sphenoid bone or sella turcica, particularly in patient with a compromised immune system, and from these locations secondarily spread into the subarachnoid space causing meningitis or abscess. Noninfectious inflammation may involve the mucosa or vasculature on the mucosa, including Wegener's granulomatosis or Bechet's disease [19]. However, these inflammatory disorders frequently involve other systemic organs and may not develop exclusively within the rhinonasal region.

Anatomy at the nose-brain interface

Connections between nasal epithelium and the brain

The nasal epithelium in the superior, middle, and inferior turbinates is in direct communication with the subarachnoid space of the brain [20]. This connection is not widely recognized but it is relevant for drug delivery to the CNS via the nasal route. Olfactory sensory neuron fibers pass through (i) the olfactory bulb located just beneath the frontal lobes of the brain, (ii) subarachnoid space underneath the frontal lobes, and (iii) the cribriform plate of the ethmoid bone, entering and innervating the nasal epithelium [21]. Cerebrospinal fluid that drains through these structures potentially carries antigens from the brain to the cervical lymph nodes for immune sensitization [22]. Higher

molecular weight proteins, such as α-synuclein, have been identified in the cerebrospinal fluid of patients with Parkinson's disease and rapid eye movement sleep behavior disorder [23].

The cribriform plate and the olfactory nerve

There are at least 5 anatomic variants of the cribriform plate, with different surface areas, and prominence of the crista galli, as well as depth from the adjacent orbital plates of the frontal bone bordering either side [21]. This perforated bony plate is a part of ethmoid bone and has multiple olfactory foramina to allow neuronal fibers to pass from the nasal cavity to the olfactory bulbs located at the base of the frontal lobes [24]. The ethmoidal slits are located anteriorly and medial to the Crista Galli, while the cribroethmoidal foramina and anterior ethmoidal foramina are additional openings located anterolaterally at the cribriform plate [24]. The associated olfactory nerves play a major role in human olfaction. Projections to piriform cortex, amygdala and entorhinal cortex enable the interpretation of smell signals with accompanying emotional valence [25]. Pathological conditions include (i) inflammatory disorders such as rhinitis, sinusitis and nasal polyps, (ii) head trauma resulting in anosmia from fracture of the cribriform plate and damage to the olfactory bulbs, (iii) meningioma arising from the olfactory groove, and (iv) anosmia associated with neurodegenerative disease such as α-synucleinopathies (Parkinson's disease, Lewy body dementia and multisystem atrophy) and tauopathy (Alzheimer disease and progressive supranuclear palsy) [26-29].

Pharmacokinetic considerations in transnasal drug delivery

Transnasal drug delivery is an increasingly recognized route for administering neurotherapeutic agents, particularly for those that require rapid onset or bypassing the gastrointestinal tract for improved bioavailability (**Figure 2**; **Table 1**). It involves the absorption of drugs through the nasal mucosa and can be utilized to achieve biological effects in both CNS and the rest of the body. Understanding pharmacokinetic considerations is essential to optimizing the efficacy of transnasal drug delivery. Relevant issues include absorption, bioavailability, formulation, distribution, metabolism, elimination, and patient-related factors.

Drugs applied to the nasal mucosa can be disseminated into the CNS via a number of routes. First, the olfactory/nasal lymphatic route provides an extracellular conduit for intranasally administered drugs to penetrate the cerebrospinal fluid, which are then secondarily distributed to brain tissues via the dynamic exchange system between cerebrospinal fluid and interstitial fluid systems [30, 31]. Lipophilic drugs and those with a smaller molecular weight, positive charge or both, clearly have an advantage. This route also bypasses the BBB blocking both intravenously and orally applied drugs, as well as the first pass metabolism encountered by the latter. Second, there are 2 types of intracellular transport mechanisms. Drugs can be taken up by the epithelial or other supportive cells by macropinocytosis for transcellular delivery into the cerebrospinal fluid space or olfactory bulb (**Figure 2** inset) [30, 31]. This mechanism is slower than the extracellular route and may take several hours. Transneuronal transport via the olfactory and trigeminal neurons is even slower, which is in the order of days [30, 31]. Regardless, large molecular weight peptide and proteins can be delivered via these two transcellular routes [30, 31].

The bioavailability of drugs applied via the transnasal route has an advantage by avoiding both BBB and first pass metabolism. However, the amount that can be delivered to achieve a neurotherapeutic effect still needs detailed pharmacokinetic characterization. Formulation of the drug in solution or suspension can alter absorption and therefore affect its bioavailability. Adhesion to the nasal mucosa, encapsulation in carriers, and development of prodrugs that can be more readily transported are strategies being explored to increase absorption and bioavailability [31, 32].

Drug distribution in the cerebrospinal and interstitial fluids are determined by bulk flow of these fluids in the brain. The flow rate of cerebrospinal fluid is about 20 cc/hour, compared to 50 cc of blood per 100 grams of brain tissue per minute. These rates may accelerate during the non-rapid eye movement phase of sleep and yawning [33, 34]. Therefore, distribution of a drug may increase during these periods. Furthermore, brain-specific metabolic pathways may alter the steady-state level of a drug in the brain. The most well-known one is monoamine oxidase that metabolizes neurotransmit-

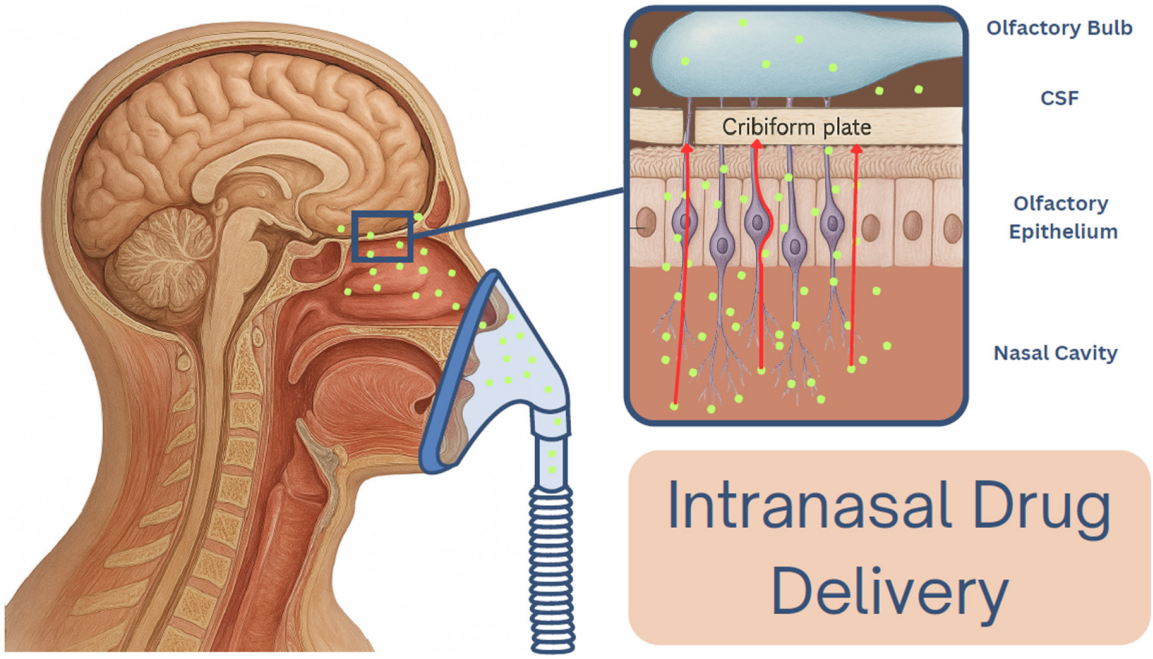

Figure 2. Transnasal delivery of drugs and biologics for brain tumor patients. High lipid solubility, low molecular weight, and positive charge are prerequisite chemical properties for drugs to diffuse into the cerebrospinal fluid via the nasal mucosa. Larger molecular weight neuropeptides and antibodies require transepithelial and transneuronal transport across the nasal epithelium, olfactory nerve, and trigeminal nerve. TTFields may facilitate this process by poration of cytoplasmic membranes. Once these drugs and biologics reach the cerebrospinal or interstitial fluid, there is a possibility of an anterior-to-posterior concentration gradient, with the frontal lobes of the brain having a higher concentration than occipital lobes.

Table 1. Drug categories for transnasal delivery to the brain, and their associated advantages and disadvantages

Drugs for Transnasal Delivery	Advantages	Disadvantages
Dexamethasone	Known pharmacodynamic effect	Unknown pharmacokinetics
	Direct route into the brain	Potential for peudotumor cerebri
	No first pass metabolism	
	High potency	
Corticorelin acetate	Known pharmacodynamic effect	Unknown pharmacokinetics
	Known steroid sparing effect	Unknown side effect on nasal epithelium
	Direct route into the brain	
	No first pass metabolism	
Checkpoint inhibitors	Known pharmacodynamic effect	Unknown pharmacokinetics
	Direct route into the brain	Unknown side effect on nasal epithelium
	No first pass metabolism	Unknown efficacy against brain tumors
Bispecific antibodies	Known pharmacodynamic effect	Unknown pharmacokinetics
	Direct route into the brain	Unknown side effect on nasal epithelium
	No first pass metabolism	Unknown efficacy against brain tumors
Antibody-drug conjugate	Known pharmacodynamic effect	Unknown pharmacokinetics
	Direct route into the brain	Unknown side effect on nasal epithelium
	No first pass metabolism	Unknown efficacy against brain tumors

ters and certain *bona fide* neuroactive metabolites and drugs, including (i) tyramine, (ii) antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine

reuptake inhibitors and tricyclic antidepressants, (iii) stimulants such as amphetamines and methylphenidate, (iv) opioids such as meperidine, fentanyl and tramadol, and (v) sympathomimetics including pseudoephedrine and ephedrine [35]. Other pathways that metabolize amino acids, glucose and fatty acids may also alter the bioavailability of drugs that are delivered into the brain [36]. Lastly, P-glycoprotein and multidrug resistance-associated protein efflux pumps can expel drugs out of the brain into cerebral circulation [14, 15], so that eventually they can be detoxified and eliminated by the liver and kidneys.

The function and activation of the olfactory/nasal lymphatic route is affected by the patient-related factors such as age, genetic background, sleep-wake cycle, and body posture. Older patients have decreased cerebrospinal fluid and cerebral blood flows [37], and therefore they have altered drug pharmacokinetic profiles in the brain. A patient's pharmacogenomic profile may also result in polymorphism of P-glycoprotein and multidrug resistance-associated protein pumps with different steady-state constants. Sleep-wake cycle affects the BBB permeability, and abnormal sleep architecture may alter the amount of drug delivery into the brain [38]. Lastly, certain body postures may facilitate glymphatic transport in the brain, with the lateral posture showing better clearance of amyloid β from the brain in a rodent model [39]. Therefore, specific patient-related factors should not be discounted in the design of device for transnasal drug delivery.

Pharmacodynamic considerations in transnasal drug delivery

Although the focus of transnasal drug delivery is to bypass both BBB and first pass hepatic metabolism of a drug, there are still pharmacodynamic issues that require thoughtful considerations. They include (i) the therapeutic target and (ii) the intermediary target. Small molecules that possess the pharmacological profile for CNS penetration (molecular weight <300 grams/mol and Log P >1) have limited space for attachment of functional groups to enhance inhibition or activation at the therapeutic target [40]. Attachment of functional groups may improve specificity while inadvertently increasing the molecular weight and lowering lipid solubility requirements. For neuropeptides and antibodies, an intermediary pharmacodynamic target may be required for transepithelial and transneuronal transport across the nasal epithelium, olfactory nerve, and trigeminal nerve [31]. These intermediary targets are often receptors that mediate micropinocytosis for transport across the intended cell. Once the neuropeptide or antibody is transported into the cerebrospinal fluid in the subarachnoid space or into the interstitial fluid within the brain parenchyma, the carrier needs to detach or be inert without interference with the therapeutic target. Regardless of the type of neurotherapeutic agent, pharmacodynamic targets are still important considerations in the design of transnasal drug delivery.

Transnasal delivery of specific drugs and biologics in neuro-oncology

Dexamethasone

Dexamethasone, with a molecular weight of 392.5 grams/mole and a Log *P* value of 1.83, is a fluorinated corticosteroid indispensable for the management of cerebral edema in patients with CNS malignancies [41]. It was originally synthesized by Merck and has been in use since the 1960's [42]. It is also associated with a multitude of other adverse events, including lymphopenia, opportunistic infections, glucose intolerance, skin breakdown, gastritis or gastric ulcer, and steroid myopathy [43]. Either alone or in combination, these side effects can cause additional morbidity in patients with brain tumors. Therefore, localized administration of dexamethasone may be advantageous to achieve intracranial effect while minimizing systemic toxicities.

Transnasal delivery of dexamethasone can potentially induce the desired neurotherapeutic effect to counteract cerebral edema due to rapid onset of pharmacological activity and reduction in overall dosage that minimizes systemic adverse effects. Its chemical characteristics - high lipid solubility and low molecular weight - may allow it to diffuse into the cerebrospinal fluid via the nasal mucosa. Once it is in the cerebrospinal fluid, it can permeate the interstitial space and distribute throughout the brain parenchyma, including into the tumor microenvironment. There is a possibility of an anterior-to-posterior concentration gradient of dexamethasone in the brain, with the frontal

lobes having a higher concentration of this drug than occipital lobes. As a result, greater therapeutic efficacy and earlier onset of pharmacological action may be seen for tumors located in the frontal compared to those in the occipital lobes.

Dexamethasone is a high-potency fluorinated corticosteroid that is typically given at doses range from 4 to 6 mg in a single dose to a cumulative daily dose of 24 mg daily in 3 or 4 divided doses. Transnasal delivery may reduce the absolute dosage required for reduction of cerebral edema. Although the nasal mucosa is highly vascularized and some of the drug may permeate into the systemic circulation, the lower dose applied should minimize potential systemic side effects.

Fluticasone is another fluorinated corticosteroid with a molecular weight of 444.5 grams/mole and a Log P of 2.78 [44]. It is delivered as a nasal spray for inflammation of the nasal mucosa and in 50 mcg per dose. Fluticasone has been associated with the development of pediatric pseudotumor cerebri, which is a known complication of corticosteroid use [45, 46]. In retrospective cohort analysis, it also delayed the onset of Alzheimer's dementia, and the anti-inflammatory effect in the CNS is thought to be the putative mechanism [47, 48]. Therefore, fluticasone may have an effect in the brain simply by transnasal delivery. Furthermore, systemic adrenal suppression was found in patients, but this was observed with high doses at 1,000 or 2,000 mcg/day but not 500 mcg/day [49]. Collectively, these retrospective data provide support for the transnasal delivery of fluorinated corticosteroid in patients with brain tumors.

Synthetic neuropeptide corticorelin acetate

Corticorelin acetate is a synthetic neuropeptide that was tested as an alternative to dexamethasone for brain tumors. Preclinical experiments showed that it is better than dexamethasone and temozolomide [50]. A phase 3 multi-center, placebo-controlled, randomized clinical study conducted at more than 25 sites in the United States and Canada showed that corticorelin enabled a substantial decrease in steroid usage and minimized its associated side effects in both acute and long-term treatment of patients with cerebral edema from either primary or metastatic brain tumors [51]. Efficacy assessment was based on a composite of 3 criteria, including (i) a 50 percent reduction in dexamethasone, (ii) stable or improved Karnofsky performance status, and (iii) stable or improved 10-item Neurological Examination Scores. Unfortunately, corticorelin failed to meet it primary endpoint, which is steroid sparing for 6 months. However, anecdotal evidence exists that this drug can spare dexamethasone use in selective patients and one of them is a long-term glioblastoma survivor of 23 years to this date (personal communication).

Transnasal delivery of large molecular weight peptides into the brain is possible. Although this route of administration has not been tested for corticorelin, other peptides such as octreotide and insulin have been investigated experimentally and in clinical trials. First, octreotide does not readily cross the BBB, but Lerner et al. demonstrated ionophoretic delivery into rabbits' brain via transnasal electrodes with 3 mA electrical currents [52]. As expected, post-mortem analysis by radioimmunoassay showed highest level in the olfactory bulbs with a 6-fold increase between active and passive delivery, and a gradient of 4- to 2-fold difference was found from frontal lobe to the cerebellum [52]. Furthermore, transnasal delivery of insulin was tested in MemAID, a phase 2 randomized placebo controlled clinical trial for subjects with type 2 diabetes mellitus (NCT02415556) [53]. Participants received either 40 IU of recombinant insulin (Novo Nordisk Inc., Bagsværd, Denmark) or placebo (0.4 mL bacteriostatic sodium chloride 0.9% solution) intranasally once daily before breakfast. Those who received insulin walked faster and correlative studies showed increased cerebral blood flow and decreased plasma insulin. This trial demonstrated the feasibility of delivering insulin or other neuroactive peptides into the brain for improvement in neurocognitive functions or other neurotherapeutic benefits.

Monoclonal antibodies

Nose-to-brain delivery of monoclonal antibodies has been a longstanding interest of neuroscientists and neurologists to treat neurodegenerative and neuroinflammatory diseases [54]. In an experimental stroke model using mice and rats, Correra et al. demonstrated intracerebral penetration of anti-Nogo-A mono-

clonal antibody by intranasal delivery. The antibody became detectable in the olfactory bulbs, cerebral cortex, cerebellum, brainstem and cervical spinal cord 6 hours after administration but dissipated 24 hours thereafter [55]. There was also a dose-response effect from increasing concentrations of the antibody from 10 to 100 and then to 1,000 mcg [55]. This resulted in growth and compensatory sprouting of corticofugal neurites, as well as functional neurological recovery, in rats after induction of large unilateral cortical strokes [55]. Another example is the use of anti-CD3 monoclonal antibody to attenuate microglial activation in an experimental Alzheimer's disease model in mice [56]. Treated mice demonstrated preserved neurological functions when tested in Morris water maze testing, and this effect is independent of β-amyloid deposition [56]. These encouraging preclinical data strongly indicate that nose-to-brain delivery of therapeutic antibodies is possible. Therefore, future first-in-human clinical trials of transnasal delivery of anti-cancer antibodies, such as checkpoint inhibitors, bi-specific antibodies, and antibody-drug conjugates, are warranted for intracranial malignancies.

Combination of tumor treating fields and transnasal drug delivery

Tumor Treating Fields (TTFields) are therapeutic alternating electric fields that have anti-cancer effects [57]. This therapy is approved by the United States Food and Drug Administration for the treatment of recurrent and newly diagnosed glioblastoma patients. These two approvals are based on comparable efficacy when compared to physician choice standard-of-care therapies for recurrent glioblastomas and superior efficacy when combined with maintenance temozolomide in the adjuvant setting for newly diagnosed glioblastomas [58, 59]. Finite element analysis revealed that TTFields are distributed mostly near the surface of the brain, corpus callosum, and the frontal horns of the bilateral ventricles where conductive cerebrospinal fluid draws in electric fields [60, 61]. However, the distribution of TTFields at the cribriform plate has not been studied.

TTFields can also increase the permeability of cytoplasmic and nuclear membranes. Chang et al. used electron microscopy and observed the formation of membrane pores from TTFields treatment of U87 glioma cells [62]. These pores allowed the intracellular passage of large molecular weight fluorescent Dextra-FTIC up to a size of 50 kDa [62]. This increased permeability was transient and disappeared 24 hours after the cessation of TTFields [62]. Furthermore, Chen et al. showed that TTFields disrupt the nuclear membrane of patient-derived glioblastoma cancer stem-like cells as well as U87MG, LN428, and LN827 human glioma cell lines [63]. The disrupted nuclear membrane allowed the release of micronuclei clusters into the cytoplasm, activating DNA sensors (i) cyclic GMP-AMP synthase (cGAS) and (ii) absent in melanoma 2 (AIM2) [63]. These sensors then turned on their cognate cGAS/stimulator of interferon genes and AIM2/caspase 1 inflammasomes to produce proinflammatory cytokines, type 1 interferons, and type 1 interferon-responsive genes, ultimately resulting in immunogenic cell death [63]. The induction of immunogenic cell death by TTFields is the basis for the clinical trial testing the combination of TTFields and pembrolizumab in the adjuvant setting for newly diagnosed glioblastoma patients (NCT06556563). Therefore, compared to intravenous administration of pembrolizumab, the combination of TTFields and transnasal delivery of pembrolizumab may benefit glioblastoma patients more by the transient disruption of cytoplasmic membranes to allow increased permeability of pembrolizumab into the brain for greater induction of antitumor immunity.

Our computer modeling team used finite element analysis to investigate the distribution of TTFields at or near the cribriform plate. Indeed, increased intensity was observed there (**Figure 3**), and this may help the nose-to-brain delivery of anti-tumor therapeutic neuropeptides, monoclonal antibodies, and large molecular weight drugs. We first modeled the cribriform plate using a conductivity value for trabecular bone (σ=0.084 S/m), based on density measured by computed tomography [64]. However, when compared to the value for cortical bone in the adjacent frontal skull (σ=0.021 S/m), trabecular bone has lower median electric field intensity ($E_{50\%}$) and hot spot ($E_{5\%}$), while 95% coverage ($E_{95\%}$) is similar between these two (**Figure 3A**). In contrast, power deposition, as represented by specific absorption ratio (SAR) at all ranges, including $SAR_{95\%}$, $SAR_{50\%}$, and $SAR_{5\%}$, were higher for trabecular than corti-

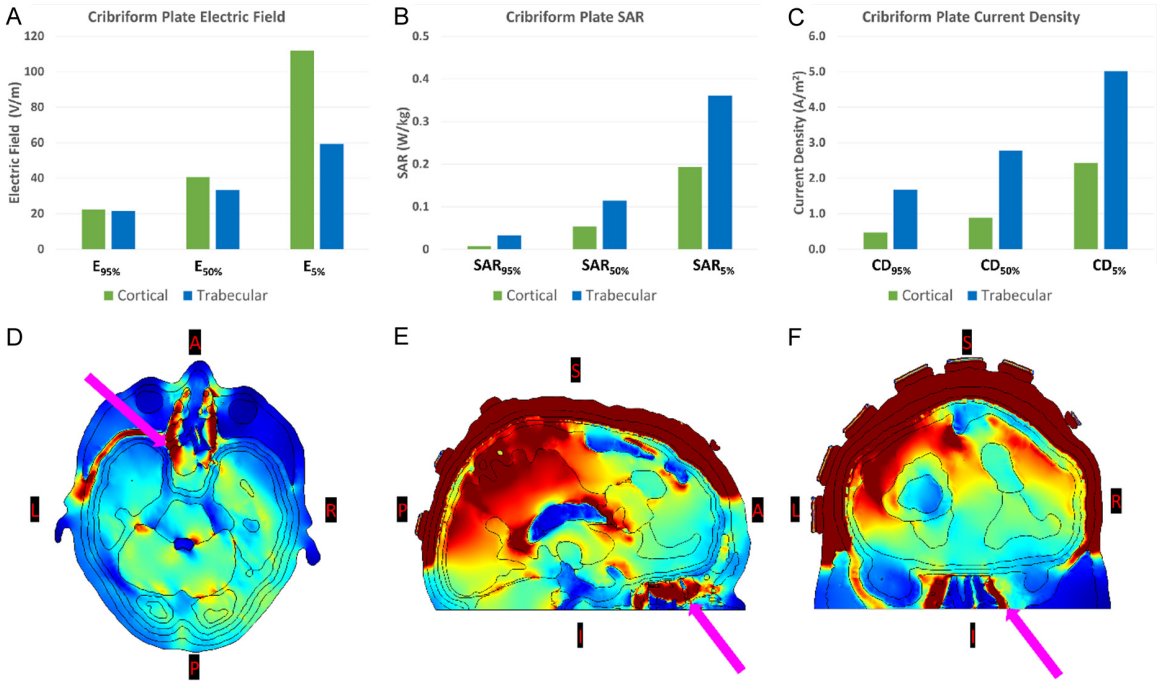

Figure 3. Finite element analysis of Tumor Treating Fields at the cribriform plate. De-identified MRI dataset was used for contouring of the cribriform plate and other intracranial structures. After conductivity values were assigned, the model was solved for electric field, specific absorption ratio, and current density. The cribriform plate was assigned a conductivity value for either trabecular (σ=0.084 S/m) or cortical bone (σ=0.021 S/m). Although Plan Quality Metrics for 95% coverage of electric field ($E_{95\%}$) was similar between trabecular and cortical bones, median electric field intensity ($E_{50\%}$) and hot spot ($E_{5\%}$) were lower for trabecular bone (A). Power deposition represented by specific absorption ratio (SAR) at $SAR_{95\%}$, $SAR_{50\%}$ and $SAR_{5\%}$ were higher for trabecular than cortical bone (B). Similar findings were observed for current density (CD) at $CD_{95\%}$, $CD_{50\%}$ and $CD_{5\%}$ (C). Representative electric field distribution at the cribriform plate was shown in the axial (D), sagittal (E) and coronal (F) slice planes (pink arrow).

cal bone (**Figure 3B**). Similar findings were observed for current density (CD) at $CD_{95\%}$, $CD_{50\%}$ and $CD_{5\%}$ (**Figure 3C**). The electric field distribution map showed high intensity at the cribriform plate in the axial (**Figure 3D**), sagittal (**Figure 3E**) and coronal (**Figure 3F**) slice planes. Together, TTFields can penetrate into the cribriform plate, potentially altering the permeability of this anatomic window and facilitating delivery of neurotherapeutics into the brain.

Conclusions

Transnasal delivery of neurotherapeutics is possible for brain tumor patients. This route has the advantage of circumventing first pass metabolism to increase bioavailability in the CNS while minimizing systemic toxicities. It can also bypass the BBB to increase the therapeutic index of neuroactive compounds, neuropeptides, and monoclonal antibodies. Dexamethasone, corticorelin, and monoclonal antibodies, such as checkpoint inhibitors, bi-specific antibodies, and antibody-drug conjugates are potentially useful drugs for the population with brain tumors. If a clinical trial can establish proof-of-concept, it will open up tremendous opportunities for testing new neurotherapeutics in neuro-oncology via the transnasal route.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Eric T Wong, Division of Hematology/Oncology, George 315, Brown University Health Cancer Institute and Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02903, USA. Tel: 401-444-4564; Fax: 401-

444-4184; E-mail: ewong1@brownhealth.org; eric_wong@brown.edu

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