Intranasal Delivery—A New Therapeutic Approach for Brain Tumors

a report by
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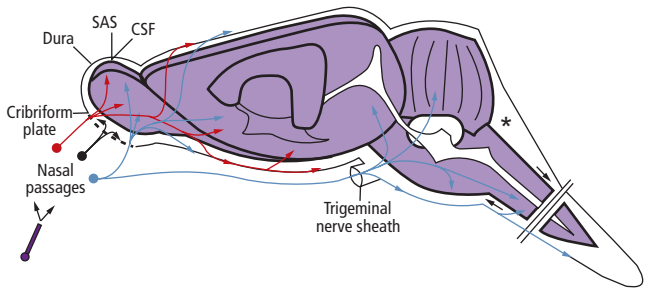
Despite significant advances in tumor imaging, neurosurgery, and radiotherapy, the prognosis for patients with malignant gliomas is extremely poor. The five-year survival rate for patients with glioblastoma (GBM), the most aggressive form of malignant glioma, is less than 5% after initial diagnosis.[1] Factors that contribute to the dismal prognosis associated with GBM include its infiltrative nature throughout the brain, which limits the effectiveness of local treatment of surgical resection and targeting of radiotherapy, and the blood–brain barrier (BBB), which limits access of systemically administered therapeutics to the tumor.

In the past decade a number of drug delivery strategies have been developed to overcome challenges presented by the BBB. In particular, direct drug administration into the brain parenchyma, such as convection-enhanced delivery (CED), has shown promising results in both animal models and clinical trials.[2–12] CED is a continuous infusion that uses a convective (versus diffusive) flow to drive the therapeutic agent throughout a larger region of tissue. This technique is well suited for the delivery of liposomes[6,9,11–15] and particulate drug carriers,[6,9,16,17] which have the potential to provide a sustained level of drug and to reach cellular targets with improved specificity. However, CED requires the use of potentially risky surgical procedures to position the catheter into the patient's brain parenchyma.[18,19] The convective flow to distribute the drug through the implanted catheter leads to measurable and significant inflammation and local edema because the drug solution infuses continuously beyond the tumor boundary into the adjacent normal brain tissue.[4,7,9] This 'spillover' of drug to unwanted brain regions may be due to the pressure gradient of the convective bulk flow of CED and could lead to neural toxicity.[20]

One technique that holds promise for bypassing the BBB to deliver drugs to the brain and eliminating the surgical risk and the spillover effect of drug to normal tissue is intranasal delivery. Intranasal delivery provides a practical, noninvasive method for delivering therapeutic agents to the brain because of the unique anatomic connections provided by the olfactory and trigeminal nerves. These nerves connect the nasal mucosa and central nervous system (CNS), allowing them to detect odors and other chemical stimuli.[21,22] Intranasally administered drugs reach the brain parenchyma, spinal cord, and cerebrospinal fluid (CSF) within minutes by using an extracellular route through perineural and/or perivascular channels along the olfactory and trigeminal nerves without binding to any receptor or using axonal transport (see *Figure 1*).[23,24] In addition to bypassing the BBB, advantages of intranasal delivery include rapid delivery to the CNS, avoidance of hepatic first-pass drug metabolism, and elimination of the need for systemic delivery, thereby reducing unwanted systemic side effects. Intranasal delivery also provides painless and convenient self-administration for patients, features that encourage its use for delivering therapeutic agents into the CNS.[25] Many therapeutic agents, including growth factors, proteins, peptides, viral vectors, liposomes, and vaccines, have been delivered to the CNS through the nasal route and applied for the treatment of CNS disorders in both animals and humans.[21,24,26–39] Thorne et al. reported that insulin-like growth factor-1 can be rapidly transported into the rat brain and upper spinal cord via the olfactory and trigeminal pathways.[21] Thorne et al. have recently reported delivery of interferon-beta-1b to the CNS in monkeys along the same neural pathways.[29] In humans, intranasal delivery of insulin has been shown to improve memory in normal adults[40] and in patients with early Alzheimer's disease[41,42] without changing blood levels of glucose or insulin.[43] Also, intranasal oxytocin has been reported to improve trust in humans.[44]

Figure 1: The Anatomical Extraneuronal Pathways Provided by the Olfactory and Trigeminal Nerves Following Intranasal Administration[21]



Intranasally applied drugs are rapidly transported into the central nervous system (CNS) tissue by the peripheral olfactory system (shown in red), connecting the nasal passages and olfactory bulb/rostal brain, and into the peripheral trigeminal system (shown in blue), connecting the nasal passages and the brainstem/spinal cord. Cistermal sampling in rats (asterisk) has demonstrated that some molecules, mostly lower-molecular-weight solutes, can rapidly enter the cerebrospinal fluid (CSF) after intranasal administration (shown in black).
SAS = subarachnoid space.
Reprinted from: Thorne RG, Pronk GJ, Padmanabhan V, Frey WH II, Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration, Neuroscience, *2004;127:481–96. Copyright © 2004, with permission from Elsevier.*

In brain tumors, anticancer agents such as methotrexate,[45] 5-fluorouracil,[46] and raltitrexed[47] have been delivered successfully to the brain using intranasal delivery. Shingaki et al. reported that intranasally delivered methotrexate reaches the CSF and reduces tumor weight in rodent glioma allografts.[48] Intranasal drug targeting to the brain of the chemotherapeutic raltitrexed is significantly higher than that with intravenous administration.[47] However, these chemotherapeutic agents do not discriminate between tumor and normal tissue. Thus, the concentrations of drug required to kill tumor cells can also lead to toxicity in normal neural tissue. To achieve

therapeutic efficacy without toxicity to normal tissue, the drugs need to preferentially target brain tumor while sparing normal tissue from damage.

Recently, two different therapeutic agents, including a glioma-adapted vesicular stomatitis virus strain, VSVrp30a,[49] and an oligonucleotide telomerase inhibitor, GRN163,[50] have been used to selectively target malignant gliomas and have shown impressive oncolytic activity without harming normal brain tissue. Both studies utilized intranasal delivery, resulting in targeted and effective delivery of the therapeutic agents to the tumor and inhibition of the tumor growth in human GBM xenografts. In addition, intranasal delivery of the telomerase inhibitor GRN163 doubled the survival time for xenografted animals without apparent toxicity. Although intranasal GRN163 delivery is extracellular, as described above, intranasal VSVrp30a likely involves viral transmission within the olfactory neural pathway to the brain. These findings support further development of intranasal VSVrp30a and GRN163 as potential therapies for brain tumor patients and perhaps as a means for treating multifocal brain tumors such as metastasis brain tumors and/or pediatric brainstem tumors, which are less amenable to potentially risky surgical procedures. Telomerase inhibitors, including GRN163, have reached the stage of clinical trials, so may soon become part of the available therapeutic armamentarium for cancer.

Given the promising results from recent animal studies, intranasal therapeutic agents would seem to be prime candidates for clinical trials in patients with brain tumors. Initial trials of intranasal perillyl alcohol have begun in patients with recurrent malignant gliomas, and a reduction in the size of the brain tumors has been reported.[51,52] ■

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