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Nanomaterials for convection-enhanced delivery of agents to treat brain tumors

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Abstract

Nanomaterials represent a promising and versatile platform for the delivery of therapeutics to the brain. Treatment of brain tumors has been a long-standing challenge in the field of neuro-oncology. The current standard of care – a multimodal approach of surgery, radiation and chemotherapy – yields only a modest therapeutic benefit for patients with malignant gliomas. A major obstacle for treatment is the failure to achieve sufficient delivery of therapeutics at the tumor site. Recent advances in local drug delivery techniques, along with the development of highly effective brain-penetrating nanocarriers, have significantly improved treatment and imaging of brain tumors in preclinical studies. The major advantage of this combined strategy is the ability to optimize local therapy, by maintaining an effective and sustained concentration of therapeutics in the brain with minimal systemic toxicity. This review highlights some of the latest developments, significant advancements and current challenges in local delivery of nanomaterials for the treatment of brain tumors.

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Introduction

Despite recent advances in drug delivery, treatment of glioblastoma (GBM), the most prevalent and aggressive form of high-grade glioma, remains a paramount challenge. The prognosis for individuals with GBM is poor and has remained essentially unchanged over the past few decades, with a median survival of 15 months. Hallmarks of GBM include diffuse infiltration, necrosis, genomic instability, drug resistance, and nearly universal recurrence [1]. Effective treatment is hindered by the presence of the blood–brain barrier (BBB), which limits the entry into the brain of most hydrophilic molecules and chemotherapeutics that are administered systemically. In overcoming these challenges, various strategies that bypass the BBB have gained momentum in the past 10 years, with an increasing understanding that enhancing tumor penetration and intracranial distribution of therapeutics are crucial for improved outcome.

Some studies suggest that BBB in tumors is 'leaky' due to increased angiogenesis and formation of abnormal vessels that result in a dysfunctional blood–brain tumor barrier (BBTB) [11]. However, outside of the GBM tumor core, the BBB mostly remains intact and functional, preventing the passage of therapeutics as observed in the healthy brain [11]. These studies suggest that the changes in BBB may not be sufficient to enhance penetration into tumors. The failure of systemically delivered agents to provide therapeutic benefit is likely due to their inability to physically cross the BBB, as well as other complex factors that contribute to their inefficacy.

Numerous ongoing studies are investigating local delivery strategies to circumvent the BBB and enhance accumulation at the tumor site. These include implantable or injectable systems with sustained drug release properties, with the goal of eliminating infiltrative GBM cells that cannot be surgically resected [1]. Unlike other delivery strategies, such as focused ultrasound [2], direct intracranial drug delivery is advantageous because it avoids interference with or disruption of the BBB. Additionally, systemic toxicity or side effects can be minimized with local drug delivery. Some of the earliest strategies included diffusion-based delivery mechanisms that involved direct injection of chemotherapeutics into the tumor resection cavity [3] or implantable polymers such as Gliadel® [4]. While these approaches provide the advantages of bypassing the BBB and minimizing systemic toxicity, the depth of distribution that can be achieved is very small, reaching only a few millimeters beyond the injection site [5]. Multiple injections can be performed, but with the increased risk of neurotoxicity and local side effects such as hemorrhage. Local delivery methods to overcome the limitation of poor brain penetration have been studied extensively and evaluated in various clinical trials. The following sections highlight key studies that utilize local delivery in combination with nanomaterials, and discuss current limitations as well as potential strategies to improve therapeutic outcome.

Convection-enhanced delivery

Convection-enhanced delivery (CED) has been shown to produce larger distribution volumes of agents infused into the brain parenchyma (Figure 1). Unlike diffusion-based methods, CED utilizes a continuous pressure gradient to drive bulk flow of agents which are infused directly into the tumor resection cavity, enabling large distribution of high drug concentrations, while avoiding systemic toxicity [6,7]. Importantly, CED can be used to distribute agents of various molecular weights and overcome the challenges of poor brain penetration. Compounds that do not penetrate the BBB, such as large molecular weight and/or hydrophilic compounds, are better candidates for CED because they remain in the brain parenchyma for a prolonged period after infusion, whereas small molecular weight and/or lipophilic agents can be readily eliminated through systemic circulation [8].

The distribution volume that can be achieved with CED depends on several parameters, including the volume and rate of infusion, physical characteristics of the infusate, and catheter design. Clinical trials involving CED have been carried out with various agents, including conventional chemotherapeutics, monoclonal antibodies, targeted ligand-toxin conjugates, and liposomal formulations [7].

Nanomaterials for local drug delivery

In addition to local delivery strategies, nanomaterials have been proposed as delivery systems to facilitate transport of therapeutic agents to the brain. These nanocarriers vary widely in composition, size and shape, with the ability to encapsulate either hydrophobic or hydrophilic molecules, including drugs, genetic material, radionuclides, and imaging agents [6]. Common examples of nanocarriers include liposomes, nanoparticles, dendrimers and micelles (Figure 2), many of which have been evaluated in combination with CED. Nanoencapsulation of therapeutic agents offers several advantages: it protects active molecules against degradation, reduces systemic toxicity, enables controlled or prolonged drug release, and provides the possibility of tumor targeting. The ideal nanocarrier should be capable of achieving high drug loading, with physicochemical characteristics—such as size, surface charge, and drug release profile—that are optimized for their intended use.

Systemic delivery of nanocarriers has been investigated to determine its potential for brain penetration. Ease of administration and the possibility of repeated dosage regimens are its main benefits. However, even with the best reported strategies to enhance transport across the BBB, intracranial accumulation of agents has been low, with about 1% of the injected dose reported to accumulate in the tumor in some cases [9,10]. Furthermore, systemic administration of nanocarriers inevitably results in abundant delivery to other tissues, such as the liver and lung, thereby increasing the risk of toxicity and undesired side effects.

For local delivery to the brain, nanocarriers must be less than 100 nm in size to facilitate penetration through the brain extracellular matrix (ECM) [12,13], neutral or negatively charged to limit non-specific binding [14]

Figure 1

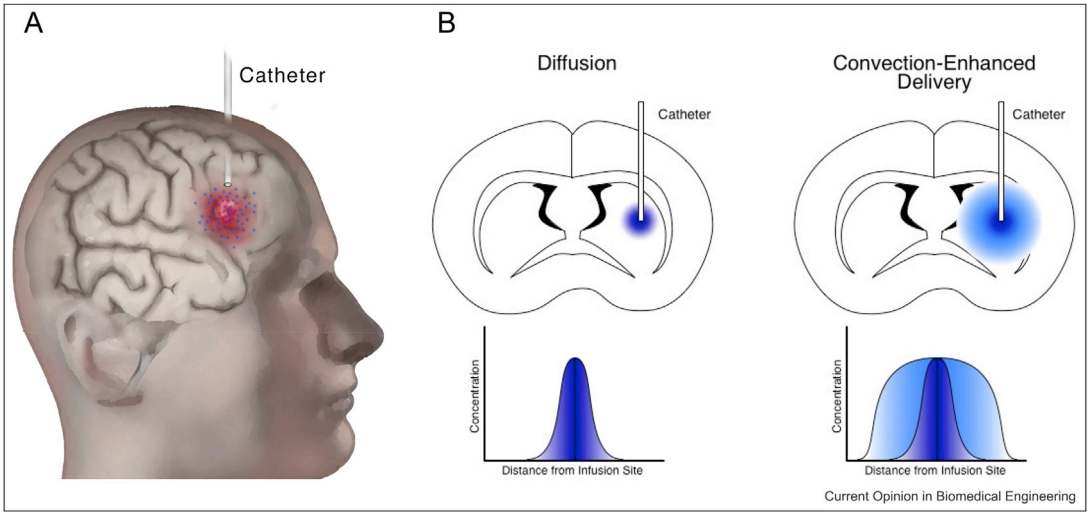

Illustration of the CED method. A) The catheter is inserted into the tumor (shown in red) or the cavity created after tumor resection, and the therapeutic agent (blue) is continuously infused using convection. B) Diffusion relies on a concentration gradient, whereas CED utilizes bulk flow kinetics, resulting in a larger distribution of agents in the surrounding tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)