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Review

Convection-enhanced delivery of nanocarriers for the treatment of brain tumors

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ABSTRACT

Primary brain tumors have a significant infiltrative capacity as their reappearance after resection usually occurs within 2 cm of the tumor margin. Local delivery method such as Convection-Enhanced Delivery (CED) has been introduced to avoid this recurrence by delivering active molecules via positive-pressure methods. For an efficient infusion, the distribution volume of the drug has to be optimized while avoiding backflow, since this is responsible for side effects and a reduction of therapeutic efficacy. The encapsulation of the drug infused in nanosized structures can be considered, which would lead to a reduction of both toxicity of the treatment and infusion time during CED. In the present review, we will firstly discuss the technical approach of CED with regard to catheter design and brain characteristics; secondly, we will describe the 'ideal' nanocarrier in terms of size, surface properties, and interaction with the extracellular matrix for optimal diffusion in the brain parenchyma. We also discuss preclinical and clinical applications of this new method.

1. Introduction

The incidence of primary central nervous system tumors (PCNST) is increasing, especially in the younger population as it represents the second cause of cancer death in adults less than 35 years of age. In the United States, about 1–2% of the population is affected and consequently suffers from profound and progressive mortality, as evidenced from the 20,500 new brain cancer cases and the 12,740 deaths estimated in 2007 [1]. A French study has described an incidence of 15.8/100,000 persons per year affected by PCNST [2]. Among the brain tumors, half originate from glial cells and are thus classified as gliomas, and more than three quarters of all gliomas are astrocytomas. Astrocytomas constitute a heterogeneous group of tumors that range from low grade to the most aggressive, glioblastoma multiforme (GBM), based on histopathological classification (from grade I to IV WHO – Word Health Organisation). GBM differs from the other cancers by its diffuse invasion of the surrounding normal tissue and its recurrence after all forms of therapy. The overall incidence of malignant glioma grades III and IV (WHO) in industrialised nations is 5–11 new cases per 100,000 people per year [3].

Conventional therapy includes surgical biopsy for pathological diagnosis and if it is possible, the first treatment is tumor resection, followed by fractioned external beam radiotherapy and systemic or oral chemotherapy [4–6]. Despite these treatments, the prognosis for patients with glioblastoma has remained largely unchanged over the last three decades. Stupp et al. described a median survival time of 14.6 months for patients treated with radiotherapy plus temozolomide which is the reference chemotherapy, and 12.1 months with radiotherapy alone [7,8]. The difficulty with treating brain tumors is the effective delivery of therapeutic agent to the tumor as well as to infiltrate cells that are not located in the tumor bed. If these outlying tissues are not treated, the tumor will reappear.

Because of the presence of the blood brain barrier (BBB), the failure of conventional systemic drug delivery for gliomas has motivated more direct approaches [9–11]. An alternative treatment is the local administration of the agent from a degradable or non-degradable polymer delivery system implanted at the site of the disease [12,13]. Although this technique presents some advantages such as sustained and controlled drug release, it is also characterized by poor drug penetration and drug dosage limited by the implant size.

Recently, it was shown that fluid convection, established by maintaining a pressure gradient during interstitial infusion, can supplement simple diffusion to enhance the distribution of small and large molecules in brain and tumor tissue. This technique called Convection-Enhanced Delivery (CED) was proposed and introduced by researchers from the US National Institutes of Health (NIH) by the early 1990s to deliver drugs that would not cross the

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BBB and that would be too large to diffuse effectively over required distances [14]. In this case, *in situ* drug concentrations can be significantly greater than those achieved by systemic administration [15,16]. This technique allows the local delivery of a wide range of substances like conventional chemotherapeutic agents [17–19], monoclonal antibodies [20,21], targeted toxins [22–24], other proteins [25], viruses [26,27], and nanocarriers [28–30]. During the first decade after the NIH researchers founded this analytical model of drug distribution, the results of several computer simulations that had been conducted according to realistic suppositions were also published, revealing encouraging results [31].

For the effective functioning of CED, the activity of the anticancer agent has to be considered but the technical drug delivery approach appears to be a critical parameter. In fact, a uniform distribution of a truly effective agent in tumors will ultimately influence the therapeutic efficacy. This is the reason why experimental protocols have to take care of different parameters proper to CED injection.

Moreover, properties of each infusate have to be considered. Nanocarriers like polymer and lipid nanoparticles, micelles, liposomes, and dendrimers are often used to vehicle some drugs that are very sensitive, toxic, or hydrophobic, or in order to target a specific organ [32]. Such nanoparticulate systems have some inner properties that have to be considered for optimal convection delivery. This review aims at firstly discussing, the technical approach of CED with regard to the materials used and the model investigated. Then the review will focus on specific properties of the infusate limiting our discussion to the use of non-viral nanocarriers such as liposomes, nanoparticles, dendrimers and micelles. Finally, animal and human trials which deliver nanocarriers in CED for therapeutic applications will be explored.

2. Technical approach of convection-enhanced delivery

2.1. Convection-enhanced delivery mechanism

Convection-enhanced delivery (CED) is a novel approach to deliver drugs into brain tissue and is defined as the continuous injection of a therapeutic fluid agent under positive pressure. This recent technique using convection or 'bulk flow' was proposed to supplement simple diffusion which characterizes local intracerebral delivery by stereotactic injections (Fig. 1). Stereotaxy is the methodology involved in the three-dimensional localization of structures within the brain, based on diagnostic image information, and the use of stereotactic frame to reach these points. Horsley and Clarke described the first use of an apparatus for neurophysiological animal experiments in 1906 and named their technique 'stereotactic' (Greek: stereo = three-dimensional (3D), taxis = to move toward) [33]. The first human stereotactic apparatus was described 40 years later by Spiegel and Wycis [34]. A stereotactic head frame is based on a 3D coordinate system consisting of three orthogonal planes, which are related to external skull points. Stereotaxy can be used to approach deep-seated brain lesions with a probe, a cannula or a high energy ionizing radiation beam [35].

Diffusion is defined as a type of passive transport (non-energy requiring) involving the movement of small molecules from an area where they are highly concentrated to an area where they are less concentrated. The diffusion of a compound in a given tissue depends mainly on 2 parameters: the free concentration gradient and the diffusivity of this compound in the tissue. With the classic diffusion technique, high molecular weight compounds (neurotrophic factors, antibodies, growth factors, enzymes) are not able to diffuse over large distances and drug distribution is very limited, thus reducing the treatment efficacy of neurological disorders [36]. For example, 3 days can be necessary for an IgG to diffuse 1 mm from its delivery site. Moreover, small drugs with good diffusion characteristics can be metabolized or quickly eliminated by capillaries reducing their diffusion in surrounding tissues [37,38]. On the contrary, CED is powered by bulk flow kinetics which occur secondary to pressure gradients. Convection, which can be used to supplement diffusion, relies on a simple pressure gradient, and is independent of molecular weight. In practice, drugs are delivered continuously via a catheter connected to a syringe pump, thus enabling the distribution of large volumes of high drug concentrations with minimum systemic toxicity (Fig. 1).

During CED, diffusion and convection take place simultaneously (Fig. 2). The phenomenon of diffusion is strictly dependent on a concentration gradient on the one hand and on the diffusivity of the infusate in a specific tissue on the other hand. Diffusion occurs all the time, but is rigorously dependent on the nature of the infusate. By CED, the agent is mainly distributed within the interstitial spaces of the tissue by convection itself. The bulk flow, which is strictly dependent on the pressure gradient, occurs throughout the establishment of the pressure gradient.

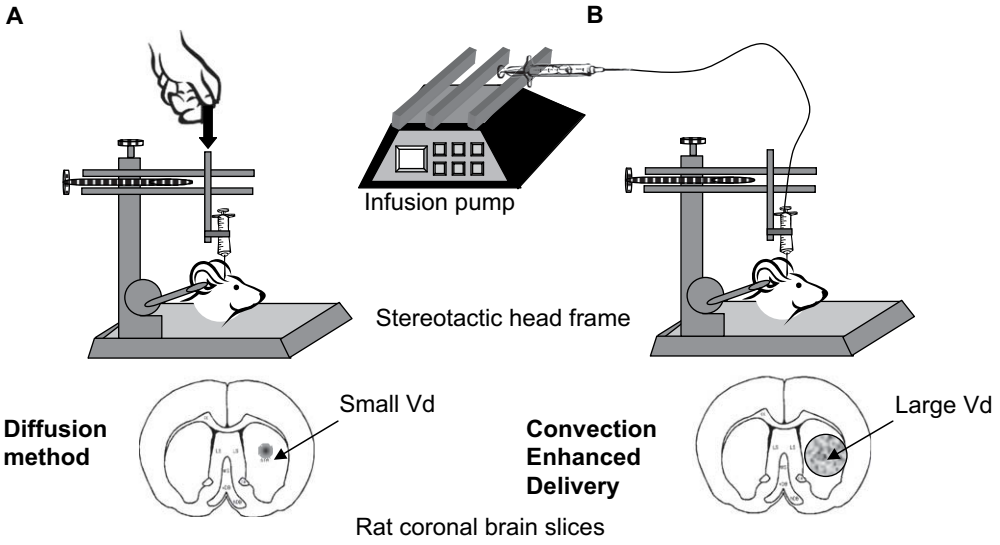

Fig. 1. Stereotactic injection in rat brain by classic diffusion method (A) versus convection-enhanced delivery (B). Infusate diffusivity is predominant in CED techniques as large volume of distribution (Vd) can be achieved compared to those obtained after a classic diffusion method.