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Review

Local delivery strategies in epilepsy; a focus on adenosine

Annelies Van Dycke *, Robrecht Raedt, Kristl Vonck, Paul Boon

Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Gent University Hospital, Belgium

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ABSTRACT

Local delivery of compounds directly into the brain may become an attractive treatment option for several neurological diseases. Higher therapeutic drug levels may be reached at the targeted brain region and in this way systemic side effects avoided. This paper provides an overview of the currently investigated experimental and clinical local delivery strategies in the brain ranging from delivery via pump mechanisms to more advanced techniques with cell and gene therapy.

The second part focuses on local brain delivery strategies for epilepsy with special attention to adenosine. Adenosine is a good candidate for local delivery techniques for epilepsy because of its proven anticonvulsive effect and it cannot be given systemically because of systemic side effects. An overview of the current published studies with local delivery of adenosine is given.

1. Introduction

Epilepsy is one of the most prevalent neurological disorders and generally requires lifetime treatment. For most patients antiepileptic drugs (AEDs) are the mainstay of the management of epilepsy.[1] However in 30% of all epilepsy patients complete seizure control cannot be achieved despite adequate treatment with AEDs or patients may suffer from unacceptable systemic side effects.[2] These patients with refractory epilepsy provide the impetus for a continuous search for alternative treatment options.

One of the underlying causes of refractoriness may be insufficient bioavailability of the AED(s) at the ictal onset region. Patients with refractory epilepsy are often resistant to a broad range of AEDs with different mechanisms of action, suggesting that nonspecific mechanisms are responsible for their limited efficacy.[3] The entrance of drugs into the brain is limited by the blood brain barrier (BBB). There is evidence that impaired drug penetration into the brain may be due to (regional) overexpression of (multi)drug efflux transporters at the site of the BBB.[3–5] Those transporters recognize a wide range of substrates, including several AEDs.[6] The prototype of these transporters is P-glycoprotein (P-gp). It is hypothesized that there is a constitutive or inherited overexpression of P-gp as a result of a genetic polymorphism[7] or that overexpression may be acquired or induced by some epilepsy-related factors such as uncontrolled seizures.[8–10]

In order to overcome the blood brain barrier – and circumventing multidrug transporters – local delivery of antiepileptic substances directly into the epileptic focus is a tempting and potentially promising strategy. This approach may reduce systemic side effects and allows to deliver larger local doses to obtain seizure control.[11]

This is an overview of the currently investigated strategies for local delivery in the brain (Table 1) with special attention to local brain delivery of adenosine for the treatment of epilepsy.

2. Strategies for local compound delivery in the brain

2.1. Intraventricular or intrathecal administration

The BBB can be bypassed by administration of drugs directly into the cerebrospinal fluid (CSF) via compound infusion through intraventricular of intrathecal catheters. Despite the fact that 100% of the administered drug reaches the brain, this administration route has several disadvantages. One major limitation is the non-uniform drug distribution throughout the subarachnoid space with very high local concentrations at the administration site and very low to zero concentrations at a distance.[11,12] Penetration from the

* Corresponding author at: Department of Neurology, 1K12, 185, De Pintelaan, 9000 Ghent, Belgium. Tel.: +32 9 332 6946; fax: +32 9 332 4971.
E-mail address: Annelies.VanDycke@UGent.be (A. Van Dycke).

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Table 1
Current local delivery strategies in the brain.

Non-biological source	Biological source
Intraventricular or intrathecal administration through catheters or via minipumps	Cell transplants
Polymeric controlled release ('wafers')	Gene therapy
Convection-enhanced delivery (CED)	
Carrier vehicles: nanoscaled particles	

CSF deep into the brain is limited, especially for high molecular weight compounds, but may be enhanced by creating a pressure gradient ('convection', see further).[13]

When a drug is injected into the cerebral ventricle, the elimination rate from the central nervous system is dependent on the cerebrospinal fluid dynamics.[12] Injection volume, osmolarity, pH, injection rate, etc. may influence this balance and have an impact on efficacy and safety of this administration route.[14] Other pitfalls with this delivery strategy are difficulties in maintaining access (e.g. catheter problems) and possible neurotoxicity.[11,15]

Direct drug delivery into the CSF is performed in the oncology domain as a form of regional chemotherapy.[11] The most commonly used application consists of continuous intrathecal infusion of baclofen or narcotics via a subcutaneous implanted pump for management of spasticity and pain. Although much experience is available with this technique, there are still possible complications mostly related to pump or catheter malfunction.[16,17]

2.2. Polymeric controlled release ('wafers')

Biocompatible synthetic polymers, impregnated with a specific compound, may be used as a source for controlled drug release in the brain. Biodegradable polymers release the compound while breaking down, whereas the matrix of non-degradable polymers remains intact after complete release of the drug. Of course the need for removal of the non-degradable polymers limits their use for clinical applications in the brain. The polymers itself are made from various materials and the complex of the polymer and the drug is mostly referred to as a 'wafer'.[18] The pharmacokinetics depend on the polymer and the characteristics of the released compound. Biodegradable polymer wafers with controlled release of carmustine ('Gliadel®' wafers) are approved for clinical use for the treatment of high-grade gliomas.[19] Since the successful development of this wafer, other chemotherapeutic agents are also used or investigated for incorporation into polymers.[20]

2.3. Convection-enhanced delivery (CED)

Poor penetration into the brain and limitation of drug dosage at the implant site are disadvantages of the intraventricular/intrathecal administration and implantation of compound-releasing wafers as described above. To overcome these problems, the technique of 'convection-enhanced delivery' (CED) has been developed.[13] CED is defined as the infusion of a therapeutic fluid via surgically implanted catheters under positive pressure. By using a syringe pump, continuous positive pressure creates a bulk flow mechanism (i.e. convection). Compared to diffusion alone, a greater distribution volume is achieved.[21,22] The precise area reached using CED depends on different factors like infusion rate, infusion volume, cannula size and compound characteristics. Especially catheter-related problems with air bubbles and backflow of the solution may interfere with the distribution area and are a challenge for the neurosurgeon.[23] It is not an approved treatment yet, but clinical trials with administration of chemotherapeutics to treat brain tumours using CED have been performed. Nanoscaled particles can also be administered via CED to obtain deep penetration of the nanoparticles into the brain parenchyma.[21]

2.4. Carrier vehicles: nanoscaled drug delivery systems

This strategy for drug delivery in the brain makes use of very small ('nano-scaled') carriers which can be administered orally, pass the BBB and release the compound into the brain. Nanoparticles are by definition smaller than 100 nm, but for medical purposes also larger particles (up to 1000 nm) are used. Because of their small size, they can penetrate cell membranes, including the BBB, and may be an ideal source for local drug delivery. The active compound can be adsorbed on the surface, enclosed in the shell or trapped inside its core.[24]

Major advantages of this strategy are the improvement of solubility of poorly water-soluble drugs, increase of the half-life of drug systemic circulation with a constant rate of drug delivery at the target zone and the reduction of systemic side effects by delivering at the target place.[25,26]

Although the use of nanoparticles seems a promising strategy, there are definitely some limitations. First, due to their physical properties there is rapid clearance of colloidal nanoparticles from the blood stream and accumulation in the liver or spleen. This may be partially solved by addition of polyethylene glycol to the surface. A second pitfall is toxicity of some nanoscaled drug delivery systems, especially in case of non-degradable particles.[27] More research on the long-term safety of nanoparticles is warranted. Meanwhile some nano-particle based therapies are in the stage of clinical trials, but not targeted to the brain. Studies for brain-delivery are still in the experimental phase.[26]

2.5. Cell transplants

Biological substances can be delivered locally in the brain via transplanted cells. In the first experimental and clinical studies, fetal cells were grafted for cell-based delivery of therapeutic compounds. Since the use of fetal cells implies many practical and ethical problems, a lot of research is done to develop a strategy where stem cells are used as a source for local delivery in the brain.[28–31] Stem cells are pluripotent cells with the ability to divide and renew themselves for indefinite periods ('long-term self-renewal') and to develop – under the right physiological or experimental conditions – into mature specialized cells, e.g. nerve cells.[32] Different types of stem cells are currently used experimentally for transplantation into the brain: embryonic stem (ES) cells, (adult) neural stem cells or induced pluripotent stem cells.[28,30]

The basic principles for cell transplantation are identical for the different cell sources. Stem cells are isolated, followed by in vitro expansion. If necessary – especially in case of embryonic stem cells – predifferentiation and/or genetic modification may be performed. Stem cells can be engineered to secrete neurotransmitters, neuromodulators or neuropeptides, making them an attractive tool in the treatment of different neurological disorders. Next, stem cells are transplanted in the host where they should survive and provide clinical benefits by local delivery of a therapeutic compound.[30,33,34]

The overall advantage of using cells for compound delivery is the lack of necessity to refill or replace pumps, polymers or carrier vehicles. A major disadvantage with cell grafting is the lack of control and the fact that only biological compounds can be delivered with this approach.

2.6. Gene therapy

Gene therapy is defined as 'the transfer of therapeutic genetic material into cells as a mean to rectify disease'.[35] Using gene