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Intrathecal delivery of protein therapeutics to the brain: A critical reassessment

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ABSTRACT

Disorders of the central nervous system (CNS), including stroke, neurodegenerative diseases, and brain tumors, are the world's leading causes of disability. Delivery of drugs to the CNS is complicated by the blood–brain barriers that protect the brain from the unregulated leakage and entry of substances, including proteins, from the blood. Yet proteins represent one of the most promising classes of therapeutics for the treatment of CNS diseases. Many strategies for overcoming these obstacles are in development, but the relatively straightforward approach of bypassing these barriers through direct intrathecal administration has been largely overlooked. Originally discounted because of its lack of usefulness for delivering small, lipid-soluble drugs to the brain, the intrathecal route has emerged as a useful, in some cases perhaps the ideal, route of administration for certain therapeutic protein and targeted disease combinations. Here, we review blood–brain barrier functions and cerebrospinal fluid dynamics and their relevance to drug delivery via the intrathecal route, discuss animal and human studies that have investigated intrathecal delivery of protein therapeutics, and outline several characteristics of protein therapeutics that can allow them to be successfully delivered intrathecally.

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1. Introduction

The World Health Organization has called neurological disorders one of the greatest threats to public health, making their treatment a critical unmet need in the current healthcare environment (World Health Organization, 2006). It is estimated that over 1 billion people worldwide suffer from a neurological disorder, including brain tumors, epilepsy, cerebrovascular diseases, neurodegenerative disorders, depression, multiple sclerosis, autoimmune encephalopathy, and chronic

Abbreviations: BBB, blood–brain barrier; CSF, cerebrospinal fluid; CNS, central nervous system; EM, electron microscopy; GAG, glycosaminoglycan; HNS, heparan *N*-sulfatase; I2S, iduronate-2-sulfatase; ICV, intracerebroventricular; IDU, α-L-iduronidase; ISF, interstitial fluid; IT, intrathecal; IV, intravenous; MC, meningeal carcinomatosis; MRI, magnetic resonance imaging.

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neuropathic pain (World Health Organization, 2006; Bray et al., 2012). Effective treatment of most of these and other neurological conditions may require the use of drugs with sites of action within the central nervous system (CNS). However, the blood–brain barrier (BBB), a protector of the CNS and a major regulator of its environment, impedes the blood-to-brain entry of most potential therapeutics.

Strategies under investigation to overcome the problem of the BBB can be roughly divided into two broad categories. The first category comprises techniques that allow or facilitate the crossing of drugs through the BBB (e.g. molecular Trojan horses, proton-coupled oligopeptide transporters, exosomes, liposomes, nanoparticles, chimeric peptides, prodrugs), while the second category consists of techniques that bypass the BBB altogether via direct delivery to the CNS (Smith et al., 2004; Alam et al., 2010; Tan et al., 2010; Guo et al., 2012; Vlieghe & Khrestchatisky, 2013). In the second category, several techniques have been investigated, including BBB disruption, and intrathecal (IT), intracerebroventricular (ICV), and intranasal delivery. This review focuses specifically on IT delivery. Because promising reports for ICV and intranasal delivery and BBB disruption have been extensively described (Alam et al., 2010; Rajadhyaksha et al., 2011; Tayebati et al., 2013; Zhao et al., 2013), we will not recapitulate them here. Instead, this review is intended to re-examine the potential of IT drug delivery to allow penetration of protein therapeutics to the brain parenchyma, a role that has been largely discounted in the past. We begin with a discussion of endogenous BBB mechanisms and CNS fluid flow dynamics, then examine current data demonstrating effective IT delivery of particular classes of therapeutic proteins to the brain. We conclude with a consideration of ideal molecules for IT delivery and promising future applications of this technology.

2. Barriers to the Delivery of Drugs to the Brain and Cerebrospinal Fluid

Drug delivery to the CNS is complicated by complex biological barriers generally termed the blood–brain barriers, including the vascular blood–brain barrier (BBB), blood–cerebrospinal fluid barrier, and specialty barriers such as the blood–retinal barrier (Neuwelt et al., 2008). These barriers serve many functions for their dependent tissue beds. The most widely known function, especially for the vascular BBB, is the prevention of the unregulated movement of substances from the blood into the CNS. Generating and maintaining stable resting potentials, action potentials, and synaptic transmission, together with the massive spatial and temporal summation of nerve impulses necessary for CNS function, requires an extreme degree of control over ionic, protein, and neurotransmitter concentrations in CNS fluids. The BBB thus affects and even regulates many of the complex interactions between the peripheral tissues and the CNS that are mediated through the blood stream, including neuroimmune interactions (Quan & Banks, 2007), feeding and energy balance (Banks, 2008), and even those affecting cognition (Banks, 2012).

The simplest mechanism by which molecules can cross the BBB is passive transmembrane diffusion. The degree to which a substance can enter by this mechanism is dictated by its lipid solubility and molecular weight, with small, lipid-soluble substances crossing more efficiently than large, hydrophilic substances. Steroid hormones are good examples of endogenous substances that can cross the BBB in this manner (Banks, 2012). Most small molecule recreational drugs also cross the BBB by this mechanism, including morphine, heroine, and ethanol (Becker & Greig, 2010). Exploitation of passive transmembrane diffusion in drug delivery has been hampered, however, by the presence of CNS-to-blood (efflux) saturable transport systems (Begley, 2004). Efflux transporters at the BBB serve critical functions, controlling electrolyte levels and limiting CNS exposure to endogenous and exogenous neurotoxins and to other endogenous biologics, including enkephalins and immunoglobulin G molecules, but they complicate the delivery of potential protein therapeutics to the CNS (Begley, 2004; Banks, 2005). We have shown, for example, that efflux of the neurotrophic peptide, pituitary adenylate cyclase-activating polypeptide 27, limits it accumulation in the brain and that inhibition of the efflux transporter allows intravenously administered peptide to accumulate in the brain to therapeutic levels (Dogrukol-Ak et al., 2009).

Influx transporters are also located at the BBB in large numbers, including those for glucose, amino acids, organic acids, vitamins, minerals, electrolytes, nucleic acids, peptides, feeding hormones, immune cells, and cytokines (Oldendorf, 1971; Davson & Segal, 1996a; Engelhardt, 2008). Use of an influx transporter by a substance can increase its brain uptake to 4- to 30-fold over what would be predicted from entry via a passive transmembrane route (Oldendorf, 1971). A few drugs are known to use endogenous, saturable influx transport systems to enter the CNS, including L-dopa, donepezil, valproic acid, and gabapentin (Pardridge, 2007). Utilizing influx transporters for drug delivery of proteins is fraught with its own special difficulties, however. For example, the proteins which transport certain ligands across the BBB are not always the same proteins which act as receptors within the CNS (Pan & Kastin, 1999). As such, a modification that enhances transport of an endogenous ligand across the BBB can also have the unwanted effect of reducing its binding affinity to its CNS receptor. Further, recombinant proteins are unpredictably sensitive to being modified. Encapsulation, alteration to the base sequence (fusion proteins), and slight changes to glycosylation patterns can cause recombinant proteins to fold improperly, lose stability, lose enzymatic activity, or become more immunogenic (Jorgensen et al., 2006; Jorgensen & Nielson, 2009; Tan et al., 2010).

Many drug delivery techniques are in development with the aim of facilitating BBB crossing, as mentioned above, although a full discussion of these is outside the scope of this review. A different strategy is direct injection of protein therapeutics into the cerebrospinal fluid (CSF) in order to bypass the BBB altogether (Patel et al., 2009; Alam et al., 2010; Rajadhyaksha et al., 2011). Administration into CSF is accomplished by injection into the lateral ventricles of the brain (ICV administration), the subarachnoid space at the level of the cisterna magna, or the lumbar spine (IT administration). Direct CNS administrations have been successfully employed in instances where a local effect of the delivered therapeutic is desired, such as in pain management, treatment of spasticity, and cancer chemotherapy. A larger extent of penetration beyond the site of injection, which is needed to treat neurodegenerative disease, is influenced primarily by the flow dynamics of the CSF.

3. Cerebrospinal and Interstitial Fluid Flow and Dynamics: Implications for Drug Delivery

A thorough understanding of the fluid flow dynamics in the brain is critical when considering the distribution patterns for protein drugs administered directly into the CNS. In the body, interstitial fluid (ISF), containing sugars, salts, lipids, amino acids, coenzymes, hormones, and cellular waste products, bathes nearly every cell, including those of the brain. ISF flow plays a key role in nutrient and waste transportation, intercellular signaling, immune regulation, and the maintenance of cellular homeostasis throughout the body. The regulation of both colloidal osmotic pressure and fluid volume is dependent upon this efficient removal of soluble proteins and waste products from the ISF (Scallan et al., 2010; Wiig & Swartz, 2012).

Within the brain ventricles, a second CNS fluid, the CSF, is continuously produced. The major direction of CSF flow is between the sites of production in the choroid plexuses (Johanson, 1988) and the major sites of reabsorption in the arachnoid villi and in the primitive lymphatic system located at the cribriform plate (Knopf et al., 1995; Boulton et al., 1999). The total volume of human CSF is about 150 mL, and the human brain produces approximately 500 mL of CSF per day (Johanson et al., 2008). It has been calculated that while the ISF is replaced relatively slowly (every 20 hours), the rate of turnover of CSF is faster and dependent on the size of the brain, with the mouse turning over its CSF

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