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Nanomaterial-mediated CNS delivery of diagnostic and therapeutic agents ☆

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ABSTRACT

Research into the diagnosis and treatment of central nervous system (CNS) diseases has been enhanced by rapid advances in nanotechnology and an expansion in the library of nanostructured carriers. This review discusses the latest applications of nanomaterials in the CNS with an emphasis on brain tumors. Novel administration routes and transport mechanisms for nanomaterial-mediated CNS delivery of diagnostic and therapeutic agents to bypass or cross the blood brain barrier (BBB) are also discussed. These include temporary disruption of the BBB, use of impregnated polymers (polymer wafers), convection-enhanced delivery (CED), and intranasal delivery. Moreover, an *in vitro* BBB model capable of mimicking geometrical, cellular and rheological features of the human cerebrovasculature has been developed. This is a useful tool that can be used for screening CNS nanoparticles or therapeutics prior to *in vivo* and clinical investigation. A discussion of this novel model is included.

Contents

1. Introduction

Recent development of nanotechnology in pharmaceutical and biomedical research has led to the creation of a number of nanostructured diagnostic and therapeutic agents, which could benefit the treatment of many central nervous system (CNS) diseases. Until recently, application of nanotechnology in the CNS has been primarily focused on brain cancer because of life-threatening risks associated with this disease. An efficient

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drug delivery to the brain tumor mass remains a challenging clinical problem. In particular, the blood–brain barrier (BBB), the blood cerebral spinal fluid, and the blood-tumor barrier all hamper the successful treatment of brain tumors by severely limiting access of therapeutic or diagnostic agents into the brain [1]. To overcome these limitations, several types of nanoparticles such as linear polymers, hyperbranched polymers, dendrimers, liposomes and micelles have been synthesized or engineered as carriers [2]. To bypass or cross the BBB more effectively, novel administration routes and transport mechanisms for nanoparticle-mediated CNS delivery have been actively explored. These include temporary disruption of the BBB to increase permeability, the use of impregnated polymers for local drug administration, convection-enhanced delivery (CED), and intranasal delivery. This review begins with a brief introduction to the BBB and then discusses the latest application of nanoparticles for the treatment and diagnosis of CNS diseases in the context of brain tumors. New routes employed for the administration of nanoparticles are also described in detail. Given the complexity of the CNS and presence of the BBB, screening and pre-optimizing nanoparticles-based agents designed to be administered systemically using an *in vitro* model could be a suitable approach prior to *in vivo* and clinical examination. A discussion of a dynamic *in vitro* (DIV) BBB model capable of mimicking features of the human BBB is included in this review.

2. The blood–brain barrier

Some speculate that strong selective pressures must have existed to allow such a complex structure as the BBB to evolve. The CNS has no lymphatic system or other way of parenchymal drainage and is enclosed within the cranium, a rigid non-expandable structure. A net influx of molecules into the CNS would increase osmolarity and allow water from the vasculature to enter the brain, leading to an elevation of intracranial pressure. Evolution of the BBB fortunately makes large increases in intracranial pressure rare occurrences. Importantly, the BBB serves to prevent potentially harmful toxins from reaching the brain.

Scientific investigation in identifying the BBB dates back to the 19th century. In 1885, Paul Ehrlich, a bacteriologist, observed that aniline dyes intravenously injected into animals colored all organs with the exception of the brain and spinal cord [3,4]. Today we know that the BBB is composed of microvascular endothelium, basement membrane and neuroglial structures such as astrocytes, pericytes and microglia. The monolayer of microvascular endothelial cells (ECs) lines the intraluminal space of brain capillaries and the ECs are packed close together, forming tight junctions. The EC layer has a luminal (inside) and abluminal (outside) compartment, separated by 300 to 500 nm of cytoplasm between the vascular system and the brain. Tight junctions consist of occludin and claudin adherent junctions and junctional adhesion molecules. There are two fundamental morphological characteristics that separate the brain from peripheral ECs. First, the cytoplasm of brain microvascular ECs has rare pinocytic vesicles — fluid-filled cell membrane invaginations that allow certain compounds to cross the BBB. These ECs also contain a greater concentration of mitochondria meeting the requirements to actively transport molecules from the blood into the brain and vice versa. Second, in addition to the structural integrity of the BBB, there exists an enzymatic surveillance system that metabolizes drugs and other compounds bypassing the structural barrier.

Achieving drug delivery across the BBB requires knowledge of both “barrier” and permeability properties of the brain ECs. In fact, several attempts to outwit the BBB are based on the molecular mimicry of molecules that are normally impermeable (e.g., glucose), yet rapidly and reliably transport across the BBB. This introduces the concept of a “biochemical BBB”, which is established by transport systems of the BBB. These can be grouped into four types:

1. *Simple diffusion.* Solute travels down a concentration gradient.
2. *Facilitated diffusion.* Solute binds to a specific membrane-spanning protein and like simple diffusion, travels down a concentration gradient.
3. *Simple diffusion via aqueous channel.* Charged ions and solutes are the principal compounds that cross the BBB by this mechanism.
4. *Active transport via protein carrier.* Solutes transport against a concentration gradient. This mechanism requires a change in the affinity of a carrier for the solute and the expenditure of ATP for transport. Vast supplies of mitochondria in the EC are thought to provide the necessary energy for this reaction.

Compounds essential to brain function are regularly transported across the BBB. The glucose transporter system at the BBB is of special importance since glucose is the primary source of energy of the brain and is required for normal brain activity and function. This system is a possible candidate for piggy-backing of molecules into the CNS via a glucose transporter (GLUT). There are five members of the sodium-independent glucose transporters, including GLUT-1 (EC), GLUT-3 (neurons) and GLUT-5 (microglia) in the brain [5]. Each transports 2-deoxyglucose, 3-O-methylglucose, mannose, galactose and glucose across the membrane [5]. GLUT-1 is a 45–55 kDa protein, depending on glycosylation state. It is present in high concentration in ECs of arterioles, venules and capillaries and facilitates D-glucose enantiomer movement from the peripheral circulation into the brain.

Another crucial transport system that operates in a similar manner is the system of multiple drug resistance [6]. Multidrug resistance protein (MDR1) has been intensely studied as a possible vehicle for drug delivery. P-glycoprotein (or P-gp, MDR1) is an efflux transporter protein found in EC, astrocytes and microglia. It is expressed on the luminal surface of the endothelial membrane and glia, and prevents toxins from entering into the brain. Many drugs are substrates for MDR1 which limits their accumulation in the brain. Vinca alkaloids, anthracyclines, and taxanes are among the anticancer agents known to be transported by P-gp. Recent work has shown that MDR1 regulation is altered by various disease conditions, and, in turn, diseases of the brain influence MDR1 expression [6,7]. An abundance of receptors at the surface of the BBB can be utilized by nanoparticles for enhanced brain uptake by coupling with receptor-specific molecules or analogues. Many other molecules such as insulin, insulin-like growth factors (IGF-1 and IGF-2) [8], leptin [9], and transferrin [10] can also get into the brain following receptor-mediated endocytosis. In general, nanoparticles should be used to by-pass efflux transport systems present at the luminal side (such as MDR1). Alternatively, nanoparticles could be substrates of those transport mechanisms enhancing the passage of specific molecules (e.g., GLUT-1) across the BBB.

3. Brain tumors

There are more than 100 types of brain tumors recognized by the World Health Organization (WHO) classified according to histopathological features, genetics, clinical presentation, and malignancy [11,12]. Gliomas include low-grade, non-malignant (WHO Grades I–II), progressively more malignant, e.g., anaplastic astrocytoma (WHO Grades III), and high-grade malignant brain tumors such as astrocytic gliomas (WHO Grade IV). There are approximately 22,000 new cases of malignant brain tumors diagnosed in the United States each year [13]. Astrocytic gliomas are either primary *de novo*, or progress from a lower grade over a 5–10 year window. Secondary brain tumors result from tumor metastases originating from peripheral locations such as the lung, breast, or the gastrointestinal tract. Secondary brain tumors are the most common in adults, accounting for 20–40% of all patients with brain tumors and outnumber primary de novo by at least 10 to 1 [11,14].

Glioblastoma multiforme (WHO Grade IV) is a devastating form of cancer that appears rapidly without much warning of prior symptoms or antecedent lower grade pathology. Hallmark characteristics of GBM include uncontrolled cell proliferation, diffuse infiltration, and resistance to apoptosis [12]. These features, at least in part, account for GBM's poor prognosis, resistance towards radio- and chemotherapy, and a mean survival of just 12–15 months [12,15]. The characterization