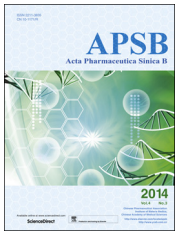
Acta Pharmaceutica Sinica B 2014;4(3):193–201

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Brain tumor-targeted drug delivery strategies

Xiaoli Wei, Xishan Chen, Man Ying, Weiyue Lu*

Department of Pharmaceutics, School of Pharmacy, Fudan University & Key Laboratory of Smart Drug Delivery (Fudan University), Ministry of Education, Shanghai 201203, China

Received 19 January 2014; revised 7 February 2014; accepted 24 February 2014

KEY WORDS

Barriers targeting;
Tumor micro environment;
Tumor cells;
Systematic targeted drug delivery

Abstract Despite the application of aggressive surgery, radiotherapy and chemotherapy in clinics, brain tumors are still a difficult health challenge due to their fast development and poor prognosis. Brain tumor-targeted drug delivery systems, which increase drug accumulation in the tumor region and reduce toxicity in normal brain and peripheral tissue, are a promising new approach to brain tumor treatments. Since brain tumors exhibit many distinctive characteristics relative to tumors growing in peripheral tissues, potential targets based on continuously changing vascular characteristics and the microenvironment can be utilized to facilitate effective brain tumor-targeted drug delivery. In this review, we briefly describe the physiological characteristics of brain tumors, including blood–brain/brain tumor barriers, the tumor microenvironment, and tumor stem cells. We also review targeted delivery strategies and introduce a systematic targeted drug delivery strategy to overcome the challenges.

*Corresponding author. Tel./fax: +86 21 51980006.
E-mail address: wylu@shmu.edu.cn (Weiyue Lu).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.apsb.2014.03.001

1. Introduction

According to the GLOBOCAN 2008, the worldwide cancer incidence of malignant brain tumors is 3.5 per 100,000 people and about 650 people are diagnosed with malignant brain tumors every day[1]. Brain tumors severely threaten human health due to their fast development and poor prognosis. Glioma, the most frequent primary brain cancer, accounts for 29% of all primary brain and CNS tumors and 80% of malignant brain tumors[2]. The median overall survival of patients with glioblastoma (GBM) is only 14.6 months after current multimodal treatment–aggressive surgical resection followed by concurrent or sequential radiation and temozolomide chemotherapies[3]. One reason why poor prognosis and rapid recurrence are associated with this standard therapy is that the infiltrate growth of gliomas makes it difficult for the surgeon to completely remove pathologic or cancer-infiltrated tissues without affecting normal brain functions[4]. Furthermore, the failure is also ascribed to the side effects of radiotherapy and poor outcome of usual chemotherapy. For many years, researchers have endeavored to deliver therapeutic agents to the tumor region effectively and reduce unnecessary drug accumulation in normal brain and peripheral tissues. For brain tumors, active targeted drug delivery systems have attracted extensive attention in recent decades. Since brain tumors possess many distinctive characteristics from peripheral tumors due to their complicated oncogenesis, many factors must be taken into consideration for effective brain tumor-targeted drug delivery, such as the barriers included in the whole process, the tumor microenvironment, and tumor cells. Now various targets have been exploited to achieve the targeting therapy using nanocarriers. Herein we provide a brief review of several possible targeting delivery strategies for brain tumors.

2. Barriers to targeted drug delivery strategies

The oncogenesis of gliomas is complicated, with various barriers preventing drug from reaching the tumor sites. There are three main barriers for brain tumor treatment: the blood–brain barrier (BBB), the blood–brain tumor barrier (BBTB), and a relatively weak EPR effect. Specific brain tumor development stages require corresponding barrier targeting treatment strategies.

2.1. *BBB targeting strategies and related drug delivery systems*

At the early stage of brain tumor development and at the infiltration growth region of the tumor, the blood–brain barrier remains intact. The blood–brain barrier, which acts as a natural guard to protect the brain from harmful substances in the blood stream while supplying the brain with the necessary nutrients for proper function, is the key challenge for delivering drugs to brain tumor[5]. The BBB is a specialized system of capillary endothelial cells which are partially covered by pericytes and basement membrane, and almost fully surrounded by the end feet of astrocytes, preventing approximately 98% of the small molecules and nearly 100% of large molecules including recombinant proteins and genes from being transported into the brain and reaching the tumor sites[6,7]. The BBB strictly limits drug transport into the brain by serving as a physical (tight junctions), metabolic (enzymes) and immunological barrier[8].

To tackle this challenge, many kinds of active targeting strategies were adopted for developing effective drug delivery systems to the brain. The active targeting systems are mainly divided into absorptive-mediated transcytosis (AMT), transporter-mediated transcytosis, and receptor-mediated endocytosis (RMT)[8].

2.1.1. *Absorptive-mediated transcytosis*

Absorptive-mediated transcytosis provides a means for the delivery of drugs across the BBB by cationic proteins or cell-penetrating peptides (CPPs). It is triggered by electrostatic interactions between the positively charged moieties of the proteins and negatively charged membrane surface regions on the brain endothelial cells[9]. Typical cationic bovine serum albumin-conjugated, pegylated nanoparticles (CBSA-NP) were prepared by Lu et al.[10] for brain targeting. They demonstrated that the permeability of CBSA-NP was about 7.76 times higher than that of BSA-NP, which offered the possibility of delivering therapeutic agents to CNS. It was reported that plasmid pORF-hTRAIL (pDNA)-incorporated CBSA-NP (CBSA-NP-hTRAIL) colocalized with glycoproteins in brain and tumor microvasculature and accumulated in tumor cells at 30 min after i.v. administration to C6 glioma bearing nude mice, *via* absorptive-mediated transcytosis[11]. Aclarubicin (ACL)-loaded cationic albumin-conjugated pegylated nanoparticles (CBSA-NP-ACL) could significantly prolong the survival of the intracranial glioblastoma-bearing mice[12]. Du et al.[13] adopted another cationic protein, wheat germ agglutinin (WGA) conjugated to the surface of liposomes and also demonstrated enhanced BBB transport.

Furthermore, alternative AMT-type cell-penetrating peptide (CPP)-based delivery systems show great ability in BBB transport. CPPs have been used to overcome the lipophilic barrier of cellular membranes and deliver a large variety of cargoes, including peptide/proteins, DNA/oligonucleotide, antibodies, imaging agents, toxins, and nanodrug carriers such as liposomes and micelles[14]. CPPs are heterogeneous in size and sequence and are positively charged. Some share common features such as an amphipathic sequence and the ability to interact with lipid membranes. The CPPs are always derived from natural proteins including the transcription-activating factor Tat, penetratin, and the Syn-B vectors, among which Tat might be the most frequently used[15]. Qin et al.[16] covalently conjugated cell-penetrating peptide TAT (AYGRKKRRQRRR) to cholesterol for preparing doxorubicin-loaded liposomes for glioma therapy. The biodistribution in the brain and heart demonstrated higher efficiency of brain delivery and lower cardiotoxicity. The survival time of the glioma-bearing rats treated with TAT-modified liposomes was significant prolonged[16]. Moreover, self-assembled polymeric micelles modified with transcriptional activator TAT peptide (TAT-PEG-*b*-Col) were constructed by Liu et al.[17] to successfully deliver antibiotics across the BBB. These studies show the potential of Tat-modified nanoparticle transport into the brain for the diagnosis and treatment of brain diseases[18].

2.1.2. *Transporter mediated transcytosis*

Since there are many kinds of transport systems in the cerebral endothelium that provide the brain with the necessary nutrients and endogenous substances, transporter mediated transcytosis takes advantage of these transport systems as a promising brain targeting strategy. Transporter mediated transcytosis is substrate-selective, so only drugs that closely mimic the endogenous substrates will be taken up and transported into the brain[6].

Glucose transporters (GLUT), which facilitate the transport of glucose from the blood to the brain, have a broad prospective use in brain targeting. Liposomes that incorporated a mannose derivative were able to cross the BBB *via* the glucose transporter GLUT1 in mouse brain[19]. Qin et al.[20] synthesized a new glycosyl derivative of cholesterol as a material for preparing novel liposomes to overcome the ineffective delivery of normal drug formulations to brain by targeting the glucose transporters on the BBB. Pharmacokinetic and distribution experiments demonstrated