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Therapeutic strategies to improve drug delivery across the blood-brain barrier

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Abstract

Resection of brain tumors is followed by chemotherapy and radiation to ablate remaining malignant cell populations. Targeting these populations stands to reduce tumor recurrence and offer the promise of more complete therapy. Thus, improving access to the tumor, while leaving normal brain tissue unscathed, is a critical pursuit. A central challenge in this endeavor lies in the limited delivery of therapeutics to the tumor itself. The blood-brain barrier (BBB) is responsible for much of this difficulty but also provides an essential separation from systemic circulation. Due to the BBB's physical and chemical constraints, many current therapies, from cytotoxic drugs to antibody-based proteins, cannot gain access to the tumor. This review describes the characteristics of the BBB and associated changes wrought by the presence of a tumor. Current strategies for enhancing the delivery of therapies across the BBB to the tumor will be discussed, with a distinction made between strategies that seek to disrupt the BBB and those that aim to circumvent it.

Keywords

blood-brain barrier; focused ultrasound; convection-enhanced delivery; P-glycoprotein

Management of most primary brain tumors includes maximal safe resection or biopsy followed by radiation and chemotherapy to target the remaining and potentially invasive tumor cells. However, delivering effective adjuvant treatment to these residual cell populations without damaging physiological brain tissue is a major challenge. One critical obstacle to effective treatments is the blood-brain barrier (BBB). This dynamic structure protects the CNS from environmental toxins and mediates physiological responses, effectively isolating the brain from the systemic circulation. Although many of the constituent cells and molecules of the BBB manifest throughout the body, in the brain they are combined into a unique construction that severely restricts entry into the brain.

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Improved drug delivery stands to enhance existing treatments, mediate tumor recurrence, and provide an opportunity to therapeutically target tumors not amenable to resection. Thus, the motivation to enhance drug delivery is powerful and has led to the development of diverse methodologies to target and evade the BBB. In this review, we discuss normal BBB physiology and pathological changes wrought by tumors, and detail therapeutic methods to disrupt, modulate, and circumvent the BBB.

Blood-Brain Barrier and Tumor-Associated Changes

The BBB refers to both passive and active mechanisms used by the brain endothelium to regulate access to the brain. This barrier is modulated in the context of brain tumors, evidenced by the penetration of Gd through the BBB on MRI of patients with glioblastoma.[98] Gadolinium enhancement increases as a function of WHO grade of astrocytoma, suggesting that BBB dysfunction is related to increasing histological grade in astrocytomas.[66] Although BBB dysfunction is observed in many gliomas, the disruption is often heterogeneous and the vasculature remains grossly intact in brain regions where infiltrating cells are found, underscoring the need for tumor-specific methods to bypass the BBB.[123] In this section we review the cellular structure of normal BBB and the impact of brain tumors on BBB coherence.

Endothelial Cells, Tight Junctions, and Extracellular Matrix

The BBB exists as a selective barrier formed by tight junctions between cerebral capillary endothelial cells, and is a critical regulator of brain homeostasis[96] (Fig. 1). Endothelial cells in the cerebral vasculature share properties with peripheral endothelial cells but also have important differences. Small gaseous molecules such as O_2 and CO_2 can diffuse through the lipid membranes of the BBB, as can small lipophilic molecules. However, the BBB tightly controls homeostasis by exclusion of harmful xenobiotics. One unique feature of brain endothelial cells is the existence of specific transport systems that regulate the entry of compounds necessary for brain metabolism, and chief among these are ATP-binding cassette (ABC) transporters. [12,52] BBB endothelial cells also have a lower number of endocytic vesicles and increased number of tight junctions, limiting transcellular and paracellular flow. Additionally, a host of intra- and extracellular enzymes provide further resistance by metabolizing substances ranging from peptides to toxic compounds.[34]

Tight junctions—the links between capillary endothelial cells—in the brain are more complex than those found in peripheral tissues and serve to prevent paracellular diffusion. Two critical components of these tight junctions are occludins and claudins. Occludins are 60- to 65-kD proteins involved in tight junction regulation that are capable of binding zona occludens protein 1 (ZO-1).[129] Claudin-3, claudin-5, and potentially claudin-12 contribute to the BBB's restriction of small ions;[125] other key components include ZO-1, ZO-2, ZO-3, cingulin, and 7H6 (Fig. 2).

Wolburg et al. found that a key component of BBB tight junctions, claudin-3, is lost in glioblastoma.[126] This finding implicated claudin-3 as an effector in the leakiness of glioblastoma vessels. There is further evidence implicating claudin-1 loss in tumor microvessels, as well as downregulation of claudin-5 and occludin in hyperplastic

vasculature. These perturbations result in a phenotypic change in BBB function due to leaky tight junctions and hyperpermeable endothelial cells.[70]

The extracellular matrix (ECM) is also modulated by tumors. Rascher et al. demonstrated that agrin, an important component of the BBB basal lamina, is absent if claudin-1, claudin-5, and occludin are downregulated.[95] The authors also noted that loss of agrin correlated with upregulation of tenascin, an ECM molecule not normally expressed in brain vessels. Although the specific mechanisms underlying alterations in tight-junction and ECM components remain unclear, these correlative studies suggest some phenotypic relationship.

Astrocytes

The neurovascular unit is formed by endothelial cells surrounded by basal lamina and astrocytic endfeet. BBB maintenance is orchestrated by astrocytes, which serve as a cellular link to neurons. From studies of astroglial-endothelial co-culture, a number of receptors, transporters, and ligands have been identified that are involved in the bidirectional induction involved in BBB maintenance.[2]

Aquaporin-4 (AQP4) is an aquaporin water channel that is believed to have an important role in glioblastoma-related edema. Astrocytes express AQP4 and Warth et al. found that AQP4 redistribution is correlated with loss of agrin in cerebral capillary basal laminae in human glioblastoma. The authors reported that the distribution of AQP4 shifted from the glial membrane in contact with mesenchymal space to cover the entire surface of glioma cells.[118] In normal astrocytes, AQP4 is arranged as orthogonal arrays of particles, but this array arrangement is lost in glioblastoma. The functional consequence of this loss of astrocyte polarization is yet unknown, but the strong evidence for the role of astrocytes in glioblastoma makes this an important topic for further investigation.

A recent study by Watkins et al. used a mouse model to demonstrate that glioma cells displace astrocytic endfeet from their position alongside endothelial cells. This is a significant breach of the BBB that disrupts communication between the astrocytes and vasculature. Glioma cells were able to co-opt regulation of vascular tone. The authors demonstrated that single glioma cells were sufficient to produce local BBB opening.[119] A study by Ndoum et al. demonstrated disruption of the astrocyte–endothelial cell association in intratumoral vessels in the enhancing regions of high-grade gliomas. Moreover, the authors found that low-grade gliomas, as well as the nonenhancing regions of high-grade gliomas, displayed intact astrocyte–endothelial cell relationships, as would be observed in unperturbed BBB.[82]

Pericytes

Cerebral pericytes are an additional component of the BBB that occupy the perivascular space. In triculture experiments with endothelial cells and astrocytes, capillary-like structures are realized. Endothelial cells that form these structures in the presence of pericytes demonstrate resistance to apoptosis, supporting a stabilizing function of pericytes in angiogenesis.[95] Further studies recapitulated the pericyte role in vascular tone, stability, repair, and angiogenesis,[64] as well as in modulation of astrocyte function.[110]

Abnormal pericyte distribution has been observed in established tumors.[78] Given that brain pericytes can support BBB function through transforming growth factor-β production, a role may exist for pericyte loss in glioma-related BBB dysfunction.[31] A more general role for pericytes in tumor vessel formation was highlighted by the discovery that glioblastoma stem cells can differentiate into pericytes during angiogenesis.[25]

P-Glycoprotein

A major player in maintaining the integrity and polarity of the BBB is through an efflux pump known as P-glycoprotein (P-gp). This 170-kD transmembrane protein belongs to the ABC transporter family and is encoded by the *ABCB1* (or *MDR1*) gene.[6] On the BBB, P-gp is localized on the apical membrane that facilitates transport in a unidirectional manner.[38,112] The expression pattern of P-gp suggests that its normal physiological role is to protect the body from xenobiotic compounds by effluxing cytotoxic molecules into luminal spaces for elimination. A characteristic feature of P-gp is broad substrate specificity. A partial list of substrates in relation to CNS tumors is summarized in Table 1.

In addition to the normal physiological role of P-gp, overexpression of P-gp is a feature common to many multidrug-resistant tumors.[55,85] P-gp expression was demonstrated in glioma, and expression levels were correlated with multidrug resistance and tumor grade.[44,68,74] In relation to the BBB, P-gp activity is disrupted at the necrotic core of glioblastoma but preserved at the tumor border.[28] This is clinically significant for glioblastoma following resection, because residual border cells with an intact barrier and potential P-gp overexpression limit drug uptake and often relapse into larger and more aggressive tumors.[26]

Therapeutic Implications

Early efforts to increase drug delivery to the brain have focused on disruption of key cellular components. However, disruptive efforts have become more refined and are joined by efforts to circumvent and modulate the BBB. In this section we detail current efforts in each of these therapeutic strategies.

BBB Disruption

Osmotic Disruption—The concept of hyperosmolar BBB disruption was first reported by Rapoport et al. in 1972.[93] Following delivery of the hyperosmotic agent, water leaves endothelial cells, resulting in shrinkage and tight-junction dysfunction, leading to increased permeability of the BBB allowing for a therapeutic window of several hours.[94] A variety of substances have been used as osmotic disruptors of the BBB, but mannitol has been most commonly used for this purpose.[1,13,17,92] Studies suggest that this method increases the concentrations of various chemotherapeutic agents in the brain up to 90-fold.[124] Furthermore, in a 1991 study of 30 patients with primary CNS lymphoma, BBB disruption via mannitol and cyclophosphamide before irradiation improved mean survival from 17.8 months to 44.5 months compared with controls receiving radiotherapy alone.[83]

There exists some debate regarding the effectiveness of this method due to conflicting reports about its differential effect on BBB permeability. Studies in multiple animal models

reported that hypertonic solutions did not selectively disrupt the BBB local to the tumor.[42,80,130] The increase in BBB permeability in a nonselective manner is problematic and raised concerns of systemic toxicity throughout the CNS.[58] Nonetheless, recent studies support the method's safety and efficacy in humans.[19,32] More work is needed to better understand the potential therapeutic value of this strategy.

MRI-Guided Focused Ultrasound—The feasibility of focused ultrasound (FUS) to disrupt the BBB was first demonstrated more than 10 years ago.[48] Subsequent studies have confirmed FUS as a valuable method to introduce focal and transient BBB disruption. [46,47] This technique has several advantages over other approaches because it is readily repeatable, noninvasive, and able to disrupt the BBB in a targeted way. Studies suggest that FUS may increase cerebrovascular permeability by producing shear stress in cells or by activation of signaling pathways involved in the regulation of permeability. [41,51,115,116] The disruption of tight junction proteins by FUS may also contribute to this method's mechanism of action.[104–106]

The technique can be used in conjunction with intravenously administered microbubbles to lower the ultrasound energy required to induce BBB disruption.[48] Nonhuman primate studies have shown that microbubble-enhanced FUS can successfully induce local BBB opening with minimal side effects.[73,75,114] The safety of FUS therapy is promising as it is not associated with significant tissue damage.[10,49,76] The use of MRI with FUS allows for the targeting and evaluation of BBB opening,[48] and several groups have developed methods that aim to monitor acoustic emissions from microbubbles in real time.[7,53,57]

Although this approach is in the preclinical phase, it is of high clinical relevance as various FDA-approved chemotherapy drugs such as doxorubicin, carmustine, trastuzumab, and temozolomide have been successfully introduced across the BBB through this approach.[8,71,77,122] Focused ultrasound has also been combined with nanoparticle platforms to enhance diagnostic and treatment capabilities. In the study by Diaz et al., gold nanoparticles were safely introduced to the tumor periphery with MRI-guided FUS in a mouse brain tumor model, augmenting surface-enhanced Raman scattering capability. Furthermore, the authors demonstrated that nanoparticles coated with anti–epidermal growth factor receptor antibody or nonspecific human immunoglobulin-G had increased uptake in glioma cells.[30]

While FUS shows promise in animal models, a limitation is signal attenuation and distortion from the skull. A study in rabbits sought to measure BBB disruption by applying FUS directly to the brain surface through a device implanted in a skull bur hole.[11] Further study is necessary to gauge the feasibility of this approach in humans.

Bradykinin Administration—Bradykinin administration has been shown to upregulate caveolin-1 and caveolin-2 at the BBB.[72] The upregulation of these compounds serves to increase endothelial cell permeability, increasing the chance of appropriate drug delivery. The potential of bradykinin, and synthetic analogs, to disrupt the BBB has been widely explored.[16,35,50,102] A central limitation is that the effect of the upregulation is exceedingly transient.[72] One clinical trial showed minimal therapeutic benefit of using carboplatin with

lobradimil, a synthetic bradykinin analog, to treat brain tumors in a pediatric population.[117] A greater understanding of the cellular mechanisms at the BBB stands to improve the efficacy of administering bradykinin with chemotherapy drugs.

Radiation-Induced Disruption—The use of radiation therapy to induce DNA damage and subsequent cell death has become an important treatment modality for brain tumors. Recent innovations in radiation therapy have improved precision, tumor definition with imaging, and radiation delivery through beam shaping.[24] In addition to its current utility, radiation therapy may play a role in selectively disrupting the BBB. Studies in both animals and humans have demonstrated that radiation therapy can induce focal BBB disruption with minimal effects on normal vasculature.[23,67,86,89] These results suggest that BBB disruption may be an additional utility of radiation therapy.

BBB Circumvention

Convection-Enhanced Delivery—Convection-enhanced delivery (CED), first described by Bobo et al. in 1994, involves the use of surgically implanted catheters that enable continuous delivery of chemotherapy directly into the tumor through positive pressure microperfusion.[18] Various antineoplastic agents, mostly immunotoxins, are under investigation for use through CED.[59,62,84,100,107] Another approach involves chemotherapeutic delivery via CED of nanoparticles.[14,128] Although these studies have demonstrated effectiveness in vivo, more work must be conducted to investigate the long-term effects of potential accumulations of the nanoparticles in the brain. CED can be used following resection or to treat inoperable tumors.[56] The major drawbacks of CED include operative risks and limited drug distribution due to backflow.[91,101,111] Despite the promise of this novel approach in enhancing the delivery of therapeutics, its safety and efficacy has yet to be clearly determined, as several Phase III clinical trials have failed to meet clinical end points.[63,87,90,99,120,121]

Viral-Mediated Circumvention—Viral vectors to deliver therapeutic drugs have also been examined for glioblastoma treatment. The goal of these strategies is to specifically target tumor cells via cell surface receptors and use virus replication derivatives to combat cancer growth. The value of using viruses as vehicles is partly due to their small size, allowing for permeability across the BBB. Such methods also have promise in combating cancers that have acquired chemotherapy and drug resistance. In vivo studies with the measles virus demonstrated a cytopathic effect on glioma stem cells and prolonging survival in a mouse model.[4] Viruses can be created with soluble peptide markers to monitor spread in vivo, and viral vectors may have synergistic activity when combined with conventional treatments, such as CED or radiation therapy.[5,27,56] Adding an amphotropic retroviral replicating vector can similarly be used to target glioma cells. Toca 511, a retroviral replicating vector, has been shown to safely deliver a cytosine deaminase gene and improve survival for glioblastoma models in vivo.[45] When combined with radiation therapy or CED, this approach has promise for future steps in combating glioblastoma growth.

Carrier Molecules—Other treatment strategies aim to use carrier molecules to transport drugs across the BBB. In creating these compounds, the surface coating can be engineered

to optimize transport and targeting abilities. Other factors such as core polymer, drug, and stabilizer formulation have also been shown to influence nanoparticle delivery.[39] Particle systems such as poly(lactic-coglycolic acid) and dendrimer nanoparticles have been studied in the context of brain cancer.[39] Another synthetic peptide, K16ApoE, carries chemotherapeutic compounds into the brain via a ligand-receptor system.[103] Although it is difficult to accurately monitor dosage, as well as systemic toxicological effects, these systems offer greater promise for drug delivery. Studies have reviewed optimal nanoparticle sizing, but future research on ligand-receptor interactions at the BBB and the ideal surface characteristics of nanoparticle delivery mechanisms is necessary.[81,127] Nanotherapeutic approaches also have used magnetic therapy to localize drug-carrying molecules.[29] In this method, a carrier molecule with iron residues is guided to the tumor location with an external magnetic field. Such an approach is encouraging, as a drug can be administered directly to the brain and with sustained release. Advances in biomaterials will also be able to increase the half-life of the encapsulated drug, improving efficacy.[29]

Liposomal Delivery—Liposomes contain a drug of interest within a lipophilic vesicle, facilitating endocytosis and uptake into brain tissue. These compounds hold great promise for glioblastoma, offering more surface area for passive diffusion. Various liposome preparations have been explored and combined with CED in previous studies.[43,60] Liposomal delivery has been extensively studied for doxorubicin, showing disease stabilization and low systemic toxicity.[36] A recent study using a rat glioma model found that the surface charge of liposomes is a significant factor for deposition within the brain.[54] The beneficial effect was noted independent of techniques disrupting BBB permeability, offering a safer and simpler method of administration. Other studies have added compounds such as wheat germ agglutinin (WGA) to the liposome surface. WGA has been shown to aid in adsorptive endocytosis in the BBB, as this glycoprotein binds to negatively charged residues in the epithelial membrane. [33] Liposomes modified with WGA have been shown to reliably target glioma tumors both in vitro and in vivo, offering a possible area of research for glioblastoma treatment. [69] Limitations of this delivery mechanism include the large size of liposomes and controlled release of the encapsulated drugs from the vesicles

Polymer Wafers—Polymer wafers that are implanted into the resection cavity after surgery allow for the localized administration of drugs that would otherwise be unable to access the tumor site due to the BBB.[21,22] This approach has renewed interest in therapeutics originally believed to be of limited use due to their inability to penetrate the BBB or due to their toxicity.[15] The Gliadel wafer (Eisai) is a critical example of this strategy and received FDA approval for use in 2003 for newly diagnosed and recurrent malignant gliomas. [9,20,56,79] However, its use is not generally recommended as subsequent studies demonstrated marginally increased survival in patients with glioblastoma and a high incidence of associated complications such as seizures, cerebral edema, and infection. Bregy and colleagues reviewed 795 patients with newly diagnosed high-grade glioma treated with Gliadel wafers in 19 studies and reported an overall complication rate of 42.7%.[20] Thus, more work must be completed to reduce complications associated with this approach and additional polymer delivery methods must be developed.

P-gp Targeting and Modulation—Modulation of specific surface proteins on capillary endothelial cells can offer more specific and less disruptive strategies to deliver drugs into the CNS. Pharmacological interventions often fail in the brain setting due in part to P-gp–mediated efflux of small molecules out of brain tissue back into the capillary lumen. Strategies have been developed to circumvent the BBB through either inhibition of P-gp or the modulation of its expression and/or trafficking.

Direct inhibition of P-gp through small molecules and other pharmaceutical methods have been initially met with limited efficacy and safety in a clinical setting; however, recent advances in drug discovery have elucidated promising new molecules with nanomolar specificity and acceptable tolerability.[65,113] The most promising drug to result from this process is tariquidar, which binds P-gp noncompetitively at nanomolar concentrations.[97] This drug has been shown to sufficiently inhibit P-gp at the BBB in vivo. Kreisl et al. showed greater uptake of 11C-N-desmethylloperamide by PET, a known P-gp substrate.[61] Acceptable tolerability is achieved in combination with dose–linear responses, tariquidar shows promise for inhibiting P-gp at the human BBB and allowing effective CNS drug delivery.

Pinzón-Daza et al. has elucidated the role of crosstalk between canonical and noncanonical Wnt pathways and its relationship to P-gp expression in the human BBB.[88] The authors found that downregulation of β-catenin led to a decrease in P-gp expression. It was also shown in vitro that the inhibition of β-catenin enhanced delivery of doxorubicin, a P-gp substrate, across a BBB epithelial monolayer against glioblastoma cells.

Modulation of P-gp has attracted much attention in disrupting the BBB in a noninvasive, specific, and rapid manner. However, despite numerous clinical trials involving P-gp inhibitors, none have been performed in any patients with primary or metastatic neoplasms of the CNS.[109] Outcomes to explore would be whether co-administration of P-gp inhibitors along with chemotherapy can stop tumor growth and/or reduce tumor size, result in prolonged survival, and result in an outcome that avoids any long-term sequelae.[3]

Conclusions

A growing body of evidence implicates the BBB as critical in fully understanding brain tumor pathophysiology. Future studies hold potential for both fundamental biological knowledge and for critical therapeutic discoveries. However, the question remains whether BBB disruption coupled with targeted therapy will improve patient survival. Several investigators across multiple disciplines are working collaboratively to improve the ability to penetrate the BBB to allow novel therapeutics to infiltrate further into the tumor and the surrounding brain.

ABBREVIATIONS

ABC	ATP-binding cassette
AQP4	aquaporin-4

BBB	blood-brain barrier
CED	convection-enhanced delivery
ECM	extracellular matrix
FUS	focused ultrasound
P-gp	P-glycoprotein
WGA	wheat germ agglutinin
ZO	zona occludens

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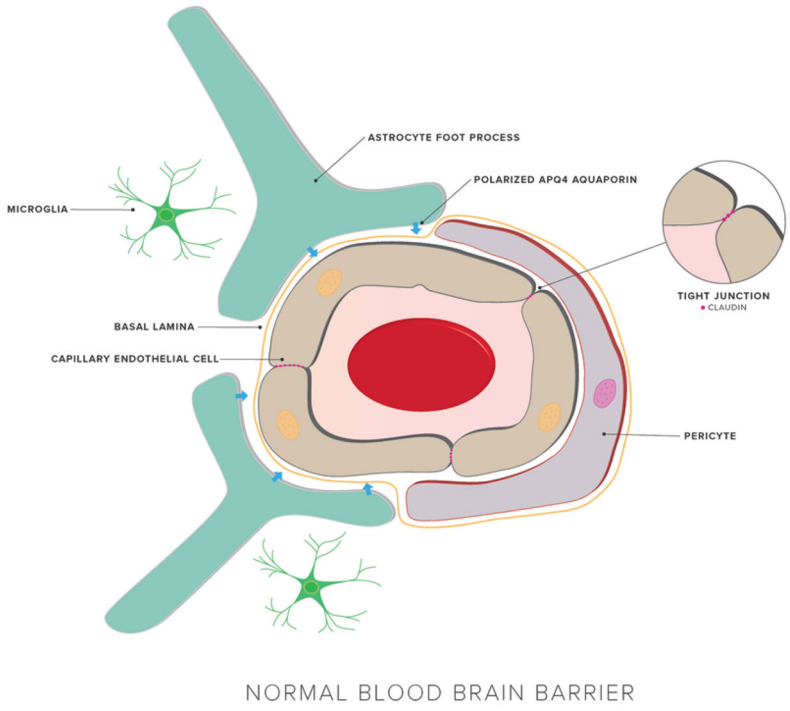

FIG. 1.

The normal, physiological BBB structure maintains strict control over CNS penetration. The major components of the BBB are cerebral endothelial cells bound together by tight junctions. The endothelium is surrounded by the basal lamina, pericytes, astrocytic endfeet, and microglia. These diverse cell types give rise to a dynamic environment that regulates entry into the brain.

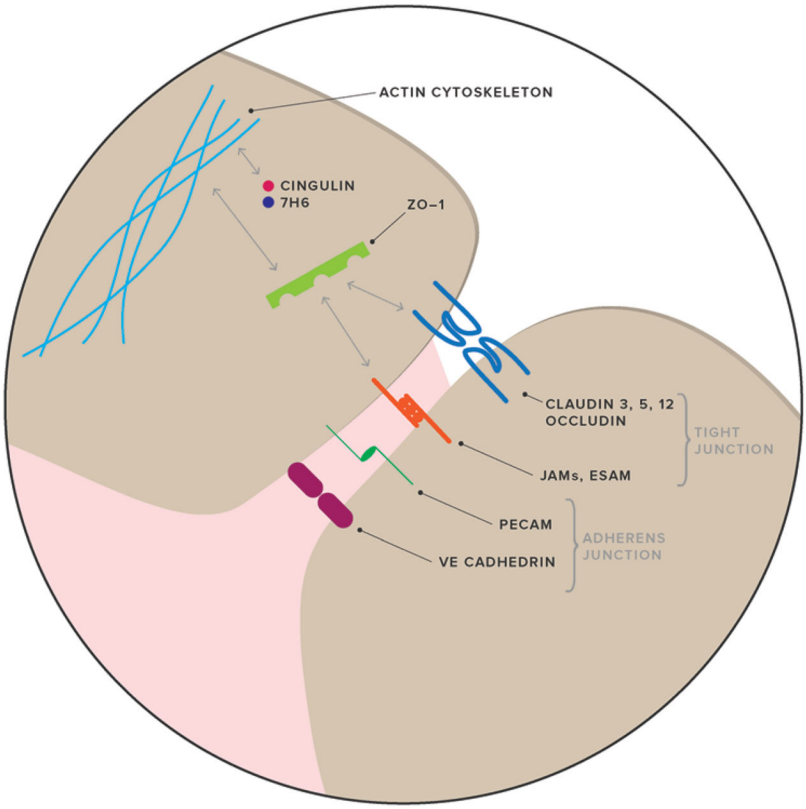

FIG. 2.

Molecular composition of the cerebrovascular endothelial tight-junction structure. Claudins and occludin are critical junctional components. Two other components of the tight junction are junctional adhesion molecules (JAMs) and the endothelial selective adhesion molecule (ESAM). ZO-1 serves as an adaptor molecule in the cytoplasm with the ability to bind membrane proteins. Other important adaptor molecules are cingulin and 7H6. These adaptor proteins, in conjunction with other regulatory proteins, foster communication between membrane junctional molecules and the cytoskeleton. A second junctional complex is the adherens junction, consisting of vascular endothelial cadherin (VE-cadherin) and the platelet–endothelial cell adhesion molecule (PECAM).

TABLE 1

Summary of current FDA-approved pharmacological treatments for CNS tumors

Drug	Indications*	Molecular Weight (Da)	*ABC* Transporter Substrate
Carmustine	Glioblastoma[37]	214	No
Cisplatin	Medulloblastoma[40]	300	*ABCC2, ABCC6*
Cyclophosphamide	Medulloblastoma	261	No
Etoposide	Glioblastoma	588	*ABCB1*
Irinotecan	Glioblastoma	586, 623 (HCl), 677 (HCl trihydrate)	*ABCB1*
Lomustine	Medulloblastoma, Grade III glioma[108]	233	No
Procarbazine	Grade III glioma	221	No
Temozolomide	Glioblastoma	194	*ABCB1*
Vincristine	Medulloblastoma, Grade III glioma	824	*ABCB1*
Bevacizumab	Glioblastoma	149,000	No

*Treatment indications collected from the literature.[37,40,108]