CellPress

Review

Antibody Approaches To Treat Brain Diseases

Vera Neves,[1,*] Frederico Aires-da-Silva,[2,*] Sofia Corte-Real,[3] and Miguel A.R.B. Castanho[1]

Recombinant antibodies are an emerging class of therapeutics with substantial promise to treat central nervous system (CNS) diseases such as Alzheimer's, Parkinson's, stroke, and brain cancers. However, poor blood–brain barrier (BBB) permeability hinders the progress of antibody therapies for conditions in which the target is located in the brain. Nonetheless, antibodies can nowadays be engineered to enhance their therapeutic applications and translocation of the BBB using the natural portals of the brain. This paper reviews advances in the development and engineering of therapeutic BBB-crossing antibodies and their high potential for treatment of CNS disorders.

Trends

Antibodies have proven utility as therapeutics, being highly selective and effective drugs to treat many diseases.

Development of antibodies to treat CNS diseases is limited by the BBB.

Several therapeutic antibodies for neurological diseases have failed to show significant clinical benefits.

Re-engineering can be used to customize antibodies to both recognize endogenous transport systems at the BBB and act as drugs in the brain.

Getting into the Brain

Central nervous system (CNS) disorders affect up to 1 billion people worldwide [1], which corresponds to around 13% of the global health burden, surpassing both cardiovascular disease and cancer [2]. Alzheimer and other dementias are estimated to constitute 3% of total deaths among neurological disorders [3]. It is estimated that 47 million people worldwide live with dementia in 2015 and, assuming that the age-specific prevalence rate remains stable, this number is expected to double every 20 years [4]. This places an enormous burden on healthcare services and society because the costs of care for dementia alone in 2015 are estimated at US$ 818 billion worldwide [5]. The low success rate observed for CNS therapeutics is mainly related to our incomplete understanding of the brain and its many functions, the susceptibility of the organ to off-target side effects, and a shortage of validated biomarkers for assessing therapeutic efficacy. Moreover, the key drawback in many cases is the low efficiency of drug delivery into the brain [6,7]. The ability to achieve consistent targeted delivery to the CNS remains a major and largely unmet challenge in the application of numerous small-molecule and biopharmaceutical drugs. Among the largest obstacles to effective CNS delivery is the BBB (Figure 1), formed by tight junctions between brain endothelial and epithelial cells that limit the transfer of therapeutic molecules between the blood and the interstitial fluid of the CNS (Box 1) [8–11].

The delivery of pharmacologically active molecules and especially macromolecules to the brain is challenged by the barrier properties. The BBB has been known for more than a century and is now recognized as a dynamic interface that, by regulating the exchange of substances between blood and brain, maintains optimal conditions for neuronal and glial function. Cerebral capillaries comprise approximately 95% of the total area of the barriers between the blood and brain and, therefore, are the main entry route for molecules into the CNS. Apart from limiting the entry of therapeutics, the BBB is also responsible for limiting the entry of immune cells and immune mediators into the CNS, which is therefore considered to be an immune privileged site. For this reason the immune responses occurring in the brain differ from those in the peripheral immune system [12]. The BBB limits not only the penetration of antibodies, immune mediators, and immune cells from the systemic circulation but also lacks the lymphatic vessels in the parenchyma to drain antigens and immune cells from the CNS to peripheral lymph nodes. In addition,

[1]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Avenida Professor Egas Moniz, 1649-028 Lisbon, Portugal
[2]Centro de Investigação Interdisciplinar em Sanidade Animal (CIISA), Faculdade de Medicina Veterinária, Universidade de Lisboa, Avenida da Universidade Técnica, 1300-477, Lisboa, Portugal
[3]Technophage SA, Avenida Professor Egas Moniz, 1649-028 Lisbon, Portugal

*Correspondence: veraneves@medicina.ulisboa.pt (V. Neves) and fasilva@fmv.ulisboa.pt (F. Aires-da-Silva).

 http://dx.doi.org/10.1016/j.tibtech.2015.10.005

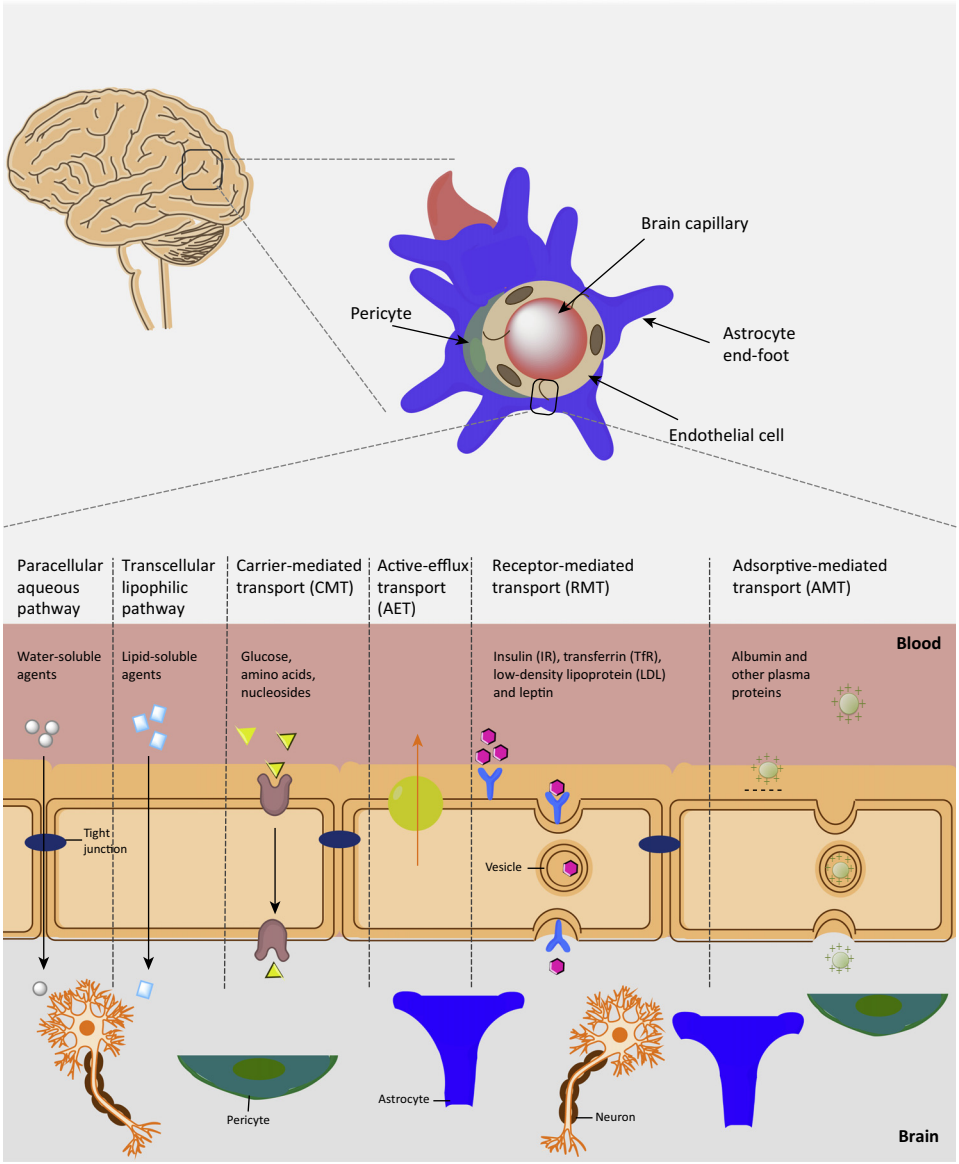

Figure 1. Brain Capillaries and the Blood–Brain Barrier (BBB). The BBB is formed by endothelial cells that interact with perivascular elements such as the basal lamina, astrocytes, neurons, and pericytes to form a functional unit. Brain endothelial cells form complex tight junctions (TJ) that seal the paracellular route, only available to small water-soluble agents. Small lipid molecules (MW <400 Da) are able to cross BBB using the transcellular lipophilic pathway. Essential molecules such as glucose, amino acids, and nucleosides are transported via carrier-mediated transport (CMT) through transport proteins. Efflux pumps move molecules out from the brain into the blood. Large molecules such as antibodies, lipoproteins, proteins, and peptides can only traverse the BBB by receptor-mediated transport (RMT). In this process a ligand interacts with a specific receptor at the apical plasma membrane (blood) of the endothelial cell. Once bound to ligand, the process of endocytosis is initiated. The receptors for iron transferrin (TfR), insulin, low-density lipoprotein (LDL), and leptin are involved in transcytosis. Finally, transcytosis might be enhanced through adsorptive-mediated endocytosis (AMT) induced by chemically transformed cationic proteins or peptides, relying on nonspecific charge-based interactions.

the features of this immune privilege site include the inability of microglial and astroglial cells to maintain immune responses, the scarcity of dendritic cells in the parenchyma, low levels of major histocompatibility complex expression, and delayed, reduced, or absent responses in the brain [13]. Although being an immune privilege site the CNS is not immune-isolated, and instead is a