Review of: "Structure of the Blood Brain Barrier and the Role of Transporters in the movement of substrates across the barriers"

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Potential competing interests: No potential competing interests to declare.

The blood-brain barrier is one of the most structurally complex membranes, with a highly selective permeability, for a good reason: the brain has to be protected from an accidental intrusion of potentially toxic chemicals, biomolecules, cells and particulates that may roam through the blood. On the other hand, controlled delivery of therapeutics to the brain renders the deployment of strategies to overcome the resistance to transport provided by this barrier necessary. Between knowing about the complexity of this barrier and understanding it from the fundamental perspective there is a giant gap, which decades of research in molecular and cell biology have attempted to fill. The review article by Singh and Vallapandian, a student and a professor, respectively, at the College of Pharmacy at the SRM Institute of Science and Technology in Tamil Nadu, attempts to provide a contribution to filling this gap.

The review article is divided to three parts. In the first, introductory part, basic anatomical features of the blood-brain barrier are provided and the function of the barrier is discussed. In the second part, individual structural elements of the barrier are described, including (a) different cells existing on the luminal and abluminal sides of the endothelial layer, e.g., pericytes, astrocytes and microglia; (b) extracellular protein structures contributing to the integrity of the barrier, e.g., claudin, occludin, zonula occludens and junctional adhesion immunoglobulins; and (c) different substructures built by these structural elements, e.g., tight junctions, adherens junctions, gap junctions and basement membranes. Finally, in the third part, different routes of transport of molecules across the barrier are being mentioned and some of the commonly used strategies to facilitate this transport are discussed.

Although the article covers mostly textbook-type information, the novice reader could still get familiarized with numerous interesting facts outside of the general realm, which are well supported by references (112 cited and 58 uncited). In turn, an expert reader could refresh knowledge about elementary or advanced facts pertaining to the complexity of the blood-brain barrier. Thus, the authors remind the reader that the barrier fulfills its function as a barrier via three distinct mechanisms: alongside serving as a crude physical barrier, it limits the transport of chemicals across it by transporting them to the luminal side and excreting them back to the blood and it also metabolizes the chemicals that it deems do not belong to the brain. Here, the reader gets acquainted with P-glycoprotein, an ATP-dependent efflux pump whose inhibition is being used today to achieve numerous effects, from enabling anticancer medications to enter the brain, as via antidepressants, to inhibiting the resistance of multidrug-resistant bacteria. The reader also learns about phosphatases,

transpeptidases and decarboxylases that break down potentially neuroactive bloodborne drugs and block them from entering the brain. The reader can also learn that because of this complex, multifaceted mechanism, an active transport across the interior of the endothelial cells of the blood-brain barrier takes more free energy than that across other endothelial barriers in the body. ATP provides sufficient energy for the transport of drugs against a negative concentration gradient and the blood-brain barrier utilizes this principle in the core of its functional makeup. In the final sentence of the abstract the authors correctly mention “the blending of the classical pharmacology with nanotechnology” as one breakthrough area from which novel methods for transporting neuroactive drugs across the blood-brain barrier will emerge, but except for one or two sentences near the end of the article, this exciting interdisciplinary area has been left untouched. On a more positive note, the reader can learn about the receptors targeted in the process of receptor-mediated transcytosis, including transferrin receptors, lactoferrin receptors, insulin receptors and low-density lipoprotein receptors.

The work by Singh and Vallapandian is a valuable compilation of information on the structure of the blood-brain barrier and the modes of transport across it. Despite the commendable effort by the authors, the article is also not the easiest of reads, as facts and arguments could have been presented somewhat more coherently. Occasional jumps between topics disturb the flow, while frequent ill word choice demands repetead reading of one sentence after another to grasp many of the points made. From the structural standpoint, the major aspect where the article fails to deliver is that of the expected congruency between the title and the content. Namely, based on the title of the article, it was expected that the division of the text to that discussing the structure of the blood-brain barrier and that discussing the role of transporters in the movement of substrates across the barrier would be more or less equal. In reality, however, the former portion of the article takes up considerably more space than the latter, which remains in great need of expansion.

In a fictional piece of literature, introducing a character in the opening and then never again bringing it to the scene comprises a transgression of standard storytelling principles. The article, likewise, begins with the mention of the blood-brain barrier as one of many blood-tissue barriers in the central nervous system and also with the definition of the cerebrospinal fluid-brain barrier, so it was naturally expected that the function and the properties of the blood-brain barrier would be compared later on against these other barriers, which did not happen to be the case. Finally, it is regrettable that the authors did not find it appropriate to supplement the description of the individual structural elements of the blood-brain barrier with a schematic image showing their interrelatedness. Usually such images take the form of a cross-section of the barrier, depicting the basal and the apical structures along with tight junctions posed in-between the individual cells.

The readers would welcome the expansion of the article and its enrichment with detail, including that derived directly from the freshest findings in the field of drug delivery across the blood-brain barrier.