EXPERT OPINION

Learning from our failures in blood–brain permeability: what can be done for new drug discovery?

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Many existing pharmaceuticals are rendered ineffective in the treatment of cerebral diseases due to a permeability barrier well known as the blood–brain barrier (BBB). Such barrier between the blood within brain capillaries and the extracellular fluid in brain tissue has motivated several approaches aimed at delivering therapeutics to the brain. These approaches rely on strategies that can be classified as molecular modifications, the use of BBB bypassing pathways, and BBB disruptions. Although several of these approaches that have been investigated so far show promising results, none has addressed the optimization of the ratio of the dose of the drug molecules that contributes to the therapeutic effects. As such, the extensive research efforts, such as prioritizing the enhancement of the BBB permeability alone is likely to fail to provide the best therapeutic effects for a given dose if prior systemic circulation is not avoided while enhancing the spatial targeting only to regions of the brain that need treatment. Hence, new therapeutics for the brain could be synthesized to take advantage of recent technologies for non-systemic delivery and spatially targeted brain uptake.

Keywords: blood–brain barrier, carrier-mediated transport, hyperthermia, nanotechnology, navigable agents, receptor-mediated transport

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1. Introduction

So far, the fact that the blood–brain barrier (BBB) prevents the brain uptake of most pharmaceutical agents makes difficult the development of new treatments of brain diseases as well as other agents for neuroimaging. But in recent years, although we witnessed encouraging results with the development of enhanced therapeutic compounds for transiting the BBB, new technological achievements that could enhance further BBB transition and targeting efficacy of drug molecules have also emerged. These new technological advancements that have remained generally ignored so far for the synthesis of new pharmaceutical agents could offer additional opportunities to efficiently transit the BBB with better targeting. This editorial suggests that investigating and combining such new complementary concepts developed outside the traditional fields of pharmaceutical research may yield promising alternatives to the development of new approaches and strategies to increase further the therapeutic efficacy through better spatial targeting to the regions of interest. As for many other approaches being proposed in pharmaceutical research, such technological opportunities should be part of the arsenal available to researchers involved in the field of drug discovery for the brain.

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2. Accessible pathways

2.1 Accessibility through the CSF

Knowing that accessibility through the CSF results in poor drug transport as it is limited by diffusion, which decreases with the square of the distance, suggests that transiting through the capillary network within the brain to reduce such a distance from the targeted site appears to be a more suitable route in this respect. Indeed, as experiments showed that small water-soluble molecules and lipid-soluble molecules decrease logarithmically (~ 10-fold decrease in drug concentration) with each mm and each 500 μm of distance respectively in the brain tissue from the CSF [1], a significant log-increase of potentially highly toxic drug molecules would need to be injected in the CSF. Such a dose-limiting approach precludes a significant drug distribution into the human brain parenchyma, which is located at a distance up to 50 mm from the CSF space.

Previous attempts with CSF-based convection-enhanced diffusion did not prove to be the best approach either as the drug distribution beyond the catheter still showed a logarithmic decrease in the brain [2].

2.2 Transmucosal, transdermal, and pulmonary pathways

Furthermore, the use of other delivery routes such as transmucosal, transdermal and pulmonary may not lead to the most efficient delivery pathways as they involve the crossing of other barriers while the quantity of drug molecules reaching the BBB would be uncertain. This is also true for most transmucosal routes such as the nasal, rectal, vaginal, ocular, and oral cavity except for intranasal pathways.

2.3 Intranasal pathways

Intranasal pathways bypass the BBB and allow the delivery of therapeutic agents to the brain [3]. Such pathways allow drug molecules that do not cross the BBB to be delivered to the central nervous system within minutes. Even for drug molecules that can cross the BBB, using intranasal pathways can reduce systemic side effects by reducing the need for the therapeutic agents to enter the systemic circulation. One of the main limitations of using the intranasal pathways is the variety in the concentration attainable in different regions of the brain and the spinal cord. Nonetheless, delivery through the intranasal pathways is an attractive and promising approach to reach the brain by bypassing the BBB.

2.4 Brain capillary pathways

Diffusion limits amplify the need to reduce the diffusion distance through prior transport of such agents in the highly distributed and dense capillary network in the brain that provides pathways leading towards the BBB location that is the closest to the target physiological site. Indeed, the diffusion constraint is bypassed in the trans-vascular route of drug delivery to the brain as the micro-vessels make up an estimated 95% of the total surface area of the BBB with a distance between capillary vessels in the brain of ~ 40 μm (for example, within such a distance, a large molecule antibody drug would diffuse within a second).

3. Diffusion methods for crossing the BBB

But for blood circulating molecules, the absence of paracellular or transcellular channels within the BBB means that they can cross the intact BBB to access the brain interstitial fluid only via lipid-mediated free diffusion, or via carrier-mediated transport (CMT) or receptor-mediated transport (RMT). Other approaches include but are not limited to the use of prodrugs, chemical drug delivery systems (CDDS), receptor/vector-mediated drug delivery, receptor-mediated transcytosis, and absorptive-mediated transcytosis.

3.1 Lipid-mediated free diffusion

For the former, almost all existing clinical drugs are lipid-soluble (< 8 hydrogen bonds with solvent water) small molecules with a molecular weight < 400 Da. Unfortunately, in practice, very few known drug molecules (~ 2%) fit such dual criteria for lipid-mediated free diffusion across the BBB [4].

3.2 Carrier-mediated transport

Although the upper pore size in the BBB that enables passive flow of molecules across is generally < 1 nm, CMT allows agents with a diameter of several nanometers to cross the BBB. In this case, the therapeutic agent is modified or re-engineered using a CMT expressed on the endothelial cells forming the BBB.

3.3 Receptor-mediated transport

Large drug molecules may be delivered across the BBB with molecular Trojan horse technology that targets the endogenous RMT systems expressed within the brain capillary endothelium. As for CMT, RMT suggests the possibility of re-engineering pharmaceuticals for BBB transport by exploiting knowledge on the endogenous RMT systems within the BBB [5].

3.4 Use of prodrugs

Prodrugs are pharmacologically inactive compounds usually synthesized to improve some deficient physicochemical properties such as membrane permeability or water solubility. As such, brain uptake of drug molecules can be improved via the use of prodrug formulations.

3.5 Chemical drug delivery

CDDS are inactive chemical derivatives of a drug aimed at providing a site-specific or site-enhanced delivery of the drug through multistep enzymatic and/or chemical transformations.

3.6 Receptor-mediated transcytosis and absorptive-mediated transcytosis

Receptor-mediated transcytosis and absorptive-mediated transcytosis are other approaches that have been investigated. Such mechanisms of transcellular transport offer encouraging possibilities to cross the BBB.

4. Beyond re-engineering pharmaceuticals

But the re-engineering process of molecular compounds can go beyond such a level of investigation. Indeed, to accelerate and extend the range of potential strategies to enable the discovery of more efficient pharmaceutical agents capable of transiting the BBB, the development of such agents can exploit methods and techniques beyond the more traditional field of pharmacology and include but not being limited to biotechnology, nanotechnology and/or instrumentation-based approaches designed to exploit specific physic phenomena.

4.1 Nanotechnology and instrument-based approaches

For instance, it is well recognized that the use of nanoparticles (NP) to deliver drugs to the brain across the BBB can provide significant advantages over currently used strategies although the temporary opening of the capillary endothelial cell tight junctions of the BBB represents another viable strategy that have been investigated with an instrumentation-based approach known as high-intensity focus ultrasound (HIFU) [6] that proved to be able to provide better volume targeting in the brain compared to other approaches such as the injection of a hyperosmotic solution.

5. Characteristics of the ideal strategy

Whatever the strategy being used, most will agree that in the longer term, an ideal approach for the delivery of therapeutics across the BBB should have the following characteristics [7]: it should be controlled; not damage the BBB; the carrier should be biodegradable and non-toxic; transport of drugs across the BBB should be selective; the drug load transported through the BBB should be adequate for reaching therapeutic concentrations in the brain while being maintained for a sufficient duration of time for the desired efficacy; and delivery should be targeted to the BBB and the site of intended action in the brain.

5.1 Shortcomings of molecular modifications alone

Although most of these characteristics could potentially be fulfilled in the future based on actual research practices, optimal targeting with the highest therapeutic index to the site that needs to be treated will still represent a real challenge if only molecular modifications including CMT-based or RMT-based molecules that could potentially benefit from advancements in biotechnology, nanotechnology, and instrumentation-related approaches, are considered.

This is particularly true if volumetric targeting is a requirement even if all efforts are put forward for the development of advanced agents synthesized to operate without external help.

5.2 Extending the arsenal to fulfill all suitable characteristics

More recent and unconventional technologies for the pharmacology research area such as the ones used in medical nanorobotics are progressing at a fast pace for extending the arsenal required to fulfill all characteristics suitable for such future pharmaceutical agents.

5.3 Volumetric targeting without systemic circulation

The introduction of medical nanorobotics in pharmacology can improve significantly volumetric targeting as in the cases with HIFU but without involving systemic circulation of the agents. Such systemic circulation is not only responsible for the increase in toxicity for the patient while affecting healthy tissues and organs as well, especially with more effective and hence toxic drug molecules, but it also results into a lower therapeutic efficacy of the dose injected.

5.4 Navigable agents

Integrating principles of robotics with nanotechnology (nanorobotics) has already proved that navigable therapeutic agents [8] were able to achieve a higher therapeutic index through the concept of direct targeting where molecules have been carried to the target specific sites using the most direct vascular route instead of being passively transported through the systemic network.

5.5 Local transient disruption of the BBB through hyperthermia

The magnetic nanoparticles (MNP) embedded in such navigable agents allowing traceability and the induction of a directional force to achieve navigation at any depth within the body when placed in a clinical MRI scanner can also be synthesized with characteristics that cause a local transient disruption of the BBB via hyperthermia. As the MNP and the therapeutic molecules share the same space, highly localized targeting in BBB permeability without systemic circulation can be achieved.

6. Conclusion

Research efforts toward drug discovery for transiting through the BBB presently use strategies that can be classified as molecular modifications, the use of BBB bypassing pathways, and BBB disruptions. The approaches relying on manipulating the molecular structures of pharmaceutical compounds is by far the most research intensive of the three categories with encouraging results already achieved and more substantial potential achievements on the horizon. But although manipulating the

Table 1. Description of the seven layers of the successful open systems interconnect (OSI) model with a potential BBB interconnect model where both cases share the same objective of delivering a payload at a target site through a complex network.

Layer	Description OSI	Description BBB
7. Application	Network process to application	Therapeutics, diagnostics, imaging
6. Presentation	Data representation	MRI contrast enhancement, etc.
5. Session	Managing sessions between applications	Scheduled multi-injections
4. Transport	Reliable delivery	Navigable agents combined with CMT-based and RMT-based molecules
3. Network	Addressing, routing for delivery on a network	Active targeting (e.g., ligands), CMT-based and RMT-based molecules
2. Data Link	Reliable point-to-point data connection	Part of the vascular network
1. Physical	E.g., electrical wires, optical cables, etc.	Blood vessels

molecular structures alone will most likely result in enhanced transports through the BBB, this strategy alone cannot yield targeting solution based on non-systemic deliveries for achieving a higher therapeutic index. Bypassing the BBB through intranasal pathways is one promising approach to avoid systemic circulation but the possibility of targeting specific regions within the brain while sparing other parts of the brain is unlikely if such a strategy is used alone. The strategies relying on BBB disruptions at a specific target site achieved with HIFU is another promising avenue to facilitate the delivery of molecular compounds to the brain. But again, systemic circulation of the drug molecules prior to transit through the BBB remains an issue. Nanorobotic-based delivery although not as mature as other strategies is presently the only approach that proposes non-systemic delivery of pharmaceutical compounds to spatially targeted regions of the BBB.

7. Expert opinion

The main motivation for considering strategies such as the use of prodrugs, CDDS, CMT, RMT, receptor/vector-mediated drug, receptor-mediated transcytosis and absorbtive-mediated transcytosis, to name but the main approaches, is the transition of the BBB. With this type of strategies relying on manipulating the molecular structures, even if one of the methods investigated proves to be extremely successful at transiting the BBB, systemic circulation of the molecular agents will remain an issue where a relatively low therapeutic index is likely to be observed. As such, two main objectives should be considered for new drug discovery for the brain namely, transport through the BBB and retention in the target volume, and non-systemic delivery with high spatial targeting efficacy that could be enhanced further with molecular-based targeting.

Presently, research efforts are in the right direction for finding solutions for many pharmaceutical compounds towards fulfilling the requirements to transit through the BBB with retention at the site of interest, and for providing practical solutions for molecular-based targeting. But without considering the synthesis of non-systemically delivered pharmaceutical compounds by integrating nano-components such as superparamagnetic iron-oxide NP as part of the molecular assembly to make such molecular compounds compatible with the future prospect of being assisted by medical nanorobotic targeting platforms to achieve direct targeting through non-systemic delivery, the targeting and therapeutic efficacy for a given dose is likely to remain far from optimal while not resolving the issue of systemic circulation. This concept of direct targeting could also be potentially beneficial for delivery through the intranasal pathways to help targeting and dosing specific parts of the brain while sparing others. Such a concept of direct targeting could be used with HIFU as well and would most probably enhance the targeting and therapeutic effect by reducing the amount of drug molecules circulating in the systemic network. Local reversible disruption of the BBB to allow the transit of larger molecular assemblies is also possible with the same magnetic NP used for direct targeting but with specifications allowing local hyperthermia. Such an approach should also be considered as a replacement to HIFU when such disruptions must be made at the exact same location as the therapeutic molecules.

But although preliminary experimental results conducted in animal models and theoretical physics agree with the fact that such a concept could enhance the transport of large molecules through the BBB while achieving a high therapeutic index, as it is often the case for other efforts in pharmaceutical research, more needs to be done to bring such a technology to a sufficient level of maturity for clinical uses. The same is true for strategies based on the new concept of direct targeting. But although such a concept of direct targeting may seem futuristic at the present time, the relatively fast progression in the field of medical nanorobotics suggests that such a complementary strategy is likely to profit in a not-too-far future, efforts and strategies being presently pursued in drug discovery for the brain.

Interesting enough is the fact that if one looks more carefully at the evolution and the trend in this field of research related to drug discovery for the brain, he will see that it begins to need an overall strategy similar to the one that was used in other highly successful technological developments such as in digital communication that led to the well-known open systems interconnect model (**Table 1**). It is a conceptual

model that characterizes and standardizes the internal functions of a communication system by partitioning it into abstraction layers where each intermediate layer serves the layer above it while being served by the layer below it. So, to attempt to answer the difficult question about what can be done for drug discovery based on our failures in blood–brain permeability, perhaps the interconnectivity between layers is the answer. In other words, if the trend continues in this particular field of research, all the required layers are likely to become sufficiently mature at some point in time in the future but the lack of interconnectivity may be the reason that will preclude the development of the best strategies. This suggests that the real challenge might not be necessary related to the more specialized sciences and technology behind the specific objective of transiting, bypassing or opening the BBB, but may be more related to the level of openness in interdisciplinary research involving new and often non-traditional concepts with more familiarized methods that together may lead to viable solutions capable of meeting all the requirements necessary to allow the widest range of molecules to target and cross effectively the BBB.

Declaration of interest

The author received research grants related to the field of medical nanorobotics with related intellectual properties. The author has no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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•• **For a recent review of nano-robotically assisted methods that could prove beneficial for drug discovery to the brain.**

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