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Commentary on “Alzheimer’s disease drug development and the problem of the blood-brain barrier”

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Abstract

The perspective by Dr. William Pardridge entitled “Alzheimer’s Disease Drug Discovery and the Problem of the Blood-Brain Barrier” makes a strong case for the imbalance in resource distribution to the drug-discovery and brain drug delivery processes, where the latter received less than 1% of the investment of the former. My own calculations are consistent with this striking imbalance. Dr. Pardridge predicts that current trials of passive immunity against β -amyloid peptide will likely fail, whereas past trials of active immunization exhibited trial-ending side effects, in part because of disruption of the integrity of the blood-brain barrier. To bring an assessment of the physiology of the blood-brain barrier and the brain delivery of drugs to the fore, several changes are needed in the way we perceive the problem, train our young scientists, organize research efforts, and incentivize reaching our common goals of effective drug therapy for Alzheimer’s disease.

Keywords

Alzheimer’s disease; Blood-brain barrier; Passive transport; Activity transport; Carrier-mediated transport

1. The Problem

Our lack of success in the development of effective therapies for brain diseases is attributable to a number of factors including, but not limited to, the complexity of the brain, the occurrence of many brain diseases in late life when many comorbid conditions exist, the lack of known targets for the treatment of many brain diseases, and in many cases, their clinical presentation years to decades after the onset of neuropathology. All of these barriers exist for the discovery and development of effective disease-modifying drugs for the delay, treatment, and prevention of Alzheimer’s disease (AD). Solutions to these issues require an enhanced investment of funds into novel research activities that address each of these issues.

However, another reason exists for the lack of development of effective drugs for AD. Our inability to deliver drugs effectively to the brain site of the disease is due in large part to our lack of attention to issues that prevent the delivery of drugs across the blood-brain barrier

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(BBB). Dr. Pardridge has written compellingly on the imbalance in resource allocation for neuroscience drug discovery versus BBB studies at both academic institutions and pharmaceutical companies.

The contention that this issue is being understudied, as indicated by Dr. Pardridge, is supported by several measures of our research effort in understanding the BBB and of our efforts to overcome it as a barrier to brain drug delivery. A simple measure of our relative lack of effort in this regard is based on an assessment of publications on the BBB and drug discovery, as well as our funding of National Institutes of Health (NIH) grants in this area. A search of PubMed for published articles using the search term “Alzheimer’s disease” produced 65,320 hits, a reflection of the broad scope of research into the causes and mechanisms of AD. A search for the terms “Alzheimer’s disease and drug therapy” produced 9842 hits, an indication of the high level of activity in drug discovery for AD at both academic and industrial institutions. In contrast, a search using the term “Alzheimer’s disease and blood-brain barrier and drug development” produced 66 hits. If these published articles reflect the level of effort devoted to the issues of the discovery of mechanisms to achieve penetration of drugs into the brain for the treatment of AD, we are devoting 0.1% of our national research effort in AD to this issue. This is completely inadequate.

Of a total of 47,000 grants currently funded by the NIH, a search of Computer Retrieval of Information on Scientific Projects (CRISP) reveals that only 21 deal specifically with the physiology of the BBB *and* mechanisms by which drugs can penetrate the BBB. In short, we are devoting a small fraction (0.4%) of our NIH budget to solving the issue of drug delivery to the brains of persons with AD.

Although the problems of transporting potentially useful drugs into the brain are large, complex, and unsolved, the potential payoff of new knowledge in the field is great. In addition to helping us produce more and better drugs to prevent, delay, or treat AD, the knowledge obtained can be applied to other chronic neurological conditions, e.g., Parkinson’s disease, Huntington’s disease, depression, various psychoses, and pain management, as well as to acute conditions that we cannot yet effectively treat, e.g., traumatic brain injury, stroke, brain damage secondary to heart attack, and damage to the central nervous system by exposure to toxins. Scientific discoveries that teach us how to deliver drugs to the brain for the treatment of AD will quickly be applied to drug delivery for other neurological conditions.

2. How do we get there from here?

Dr. Pardridge proposes that we focus on receptor mediator transporters for a number of substances, including anti- β -amyloid antibodies and neurotrophins, instead of our usual and ineffective attempts to increase the lipophilicity of compounds to achieve brain penetration. Although this is an excellent idea that he and others proposed some years ago, it is only a start. Indeed, as he remarks, comprehensive programs in the “pure science of BBB biology and the applied science of BBB drug-targeting technology” are urgently needed.

To achieve these important programs, several changes are needed in the way we perceive the problem, train our young scientists, organize research efforts, and incentivize reaching our common goals of effective drug therapy for AD.

3. National assessment of the need for BBB science and drug-delivery technology studies

Now that Dr. Pardridge and others have raised the issue of our unacceptable imbalance in resource distribution for the “pure science of BBB biology and the applied science of BBB drug-targeting technology,” a first step is to assemble the stakeholders in AD drug therapy, BBB biology, and drug delivery to affirm the extent of the problem, establish the causes of this resource distribution imbalance, and offer solutions. An NIH-sponsored meeting of the experts in the field would be a good start, followed by the creation of working groups to deal with each facet of the problems identified.

4. Enhanced training of scientists in disciplines related to BBB science and brain drug delivery

No single discipline will likely be able to solve the complex problem of drug delivery to the brain. Rather, a multidisciplinary approach is needed, including the combined efforts of bioengineers, geneticists, molecular biologists, cerebrovascular physiologists, pharmacologists, pharmacokineticists, medicinal chemists, and analytical chemists. We train too few scientists in many, if not most, of these fields, and of those trained, we do not encourage them to study BBB sciences, in part because of the lack of funding for this type of research. Specific training programs in the “pure science of BBB biology and the applied science of BBB drug-targeting technology” need to be created and funded.

5. Creation of multidisciplinary teams

Teams of researchers, now often located at disparate sites within academia and industry, need to be created and brought together, to address the brain delivery of drugs. To achieve this, funding mechanisms need to be created at the NIH and other agencies that currently do not encourage studies of the pharmacokinetics of drugs, in part because they are thought to be a purview of Big Pharma. Second, although the NIH recently encouraged multidisciplinary group applications, I am not aware of a “Request for Applications” related to such an approach in the study of brain drug delivery. Clearly such a program is needed. Further, real or perceived barriers between academia and industry need to be identified and resolved, so that the two groups can work jointly on the common problem of brain penetration by drugs. One relevant problem is a lack of clarity about the ownership of patent rights for discoveries made as part of group efforts, particularly when the individuals involved are at separate institutions.

6. Incentivizing multidisciplinary team participation

There are a number of disincentives to working as part of a team devoted to a common goal. The tenure and promotion processes at most academic institutions are better suited to assess

individual accomplishments, and based on my experience as an academic administrator, we have difficulties assessing an individual's role in group activities. As such, group activities are underappreciated and are thus a disincentive to tenure and promotion. Mechanisms by which we can quantify and incentivize group activities are urgently needed in academia.

7. Conclusions

In conclusion, the BBB is a major obstacle to the effective delivery of drugs to the brain, and our national lack of attention to this issue has slowed the development of effective drugs for the treatment of AD. As part of a national effort to prevent AD by 2020 [1], the creation of research and training programs devoted to the “pure science of BBB biology and the applied science of BBB drug-targeting technology” is critically needed.

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