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How Critical Is the Blood-Brain Barrier to the Development of Neurotherapeutics?

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The blood-brain barrier (BBB), with its charged, lipid-based, continuous basement membrane and specialized transporters, is optimized to exclude potentially threatening compounds from the central nervous system (CNS). In the setting of CNS diseases, the careful construction of the BBB is thought to restrict access of therapeutic agents that may otherwise be effective, contributing to poorer outcomes. However, there is controversy in the neurotherapeutics community about the degree to which this hypothesis is true; some argue that the BBB is not the critical factor because it naturally opens in the setting of brain pathology and that techniques to circumvent the BBB do not improve drug efficacy in many instances.¹ Moreover, some drugs do not need direct access to brain tissue in order to have their therapeutic effect. For example, fingolimod and bevacizumab are effective in patients with multiple sclerosis and glioblastoma, respectively, although their primary mechanism of action is systemic. Additionally, in some brain tumors, achieving target drug concentrations in the brain either fails to show efficacy or, in fact, causes toxicity.² In these instances, the factor impeding success of neurotherapeutics is clearly not the BBB.

That said, there is an undisputed need to ensure that adequate local drug concentrations are achieved in many brain diseases. In neuroinfectious diseases, securing the optimal clinical outcome requires achieving the minimum bactericidal concentration at the site of infection. This is true for cerebrospinal fluid and the brain parenchyma, both of which are distinct compartments.^{1,3} In Parkinson disease, the reversal of bradykinesia is only seen when adequate levels of levodopa are administered to ensure adequate concentrations in the basal ganglia.⁴ In brain cancer, temozolomide is the leading chemotherapeutic agent in treating gliomas owing in part to its favorable CNS penetration. Given the evidence that tissue

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concentration matters greatly in some CNS diseases, when drug after drug fails to achieve the desired therapeutic end points, it is tempting to blame the lack of access to the brain as the primary problem in neurotherapeutics. This is likely true for many drugs. However, to have a rational discussion about the power of the BBB to thwart effective therapeutics requires both an adequate understanding of BBB physiology and a systematic investigation of the relationship between brain-tissue concentration and therapeutic effect. To date, such investigations have rarely been undertaken because it is difficult to address the question of brain concentration and efficacy in the clinical setting.¹ Specific limitations to the investigation of this relationship include the following: (1) standardized methods to estimate drug access to the brain are lacking, (2) the few investigative tools available are invasive (ie, microdialysis or direct tissue sampling) or unsatisfying because they do not directly address the question (ie, cerebrospinal sampling), and (3) these tools often produce single data points that are insufficient because brain diseases (eg, cancer and multiple sclerosis) are heterogeneous, often exhibiting different BBB permeability within different regions of the cerebral vascular bed over time.

With recent developments in neuroimaging, we are attempting to address these limitations. Capitalizing on the wide clinical use of magnetic resonance imaging, Tofts and Kermode⁵ developed analysis techniques that may help to assess the status of the BBB noninvasively and longitudinally. The advantage of such an approach is that it could “chart” the likely ability of a given agent to enter brain tissue based on its pharmacological properties. The disadvantage is that it provides a relatively coarse measure of BBB permeability and requires speculation about the ability of any one specific drug to access brain tissue. Position emission tomography allows for a very sensitive assessment of labeled drug kinetics in brain tissue but requires the injection of a radioactive compound; in addition, a specific tracer would have to be made for each drug for maximal sensitivity and specificity. This is highly resource intensive and therefore not applicable on a wide scale. Preclinical studies of novel imaging techniques such as the mass spectrometry-based matrix-assisted laser desorption/ionization technique show promise in both visualizing drug penetration into the brain and providing temporal/spatial maps of drug distribution.⁶ If such techniques are successfully optimized for clinical translation, it may finally be feasible to assess drug delivery to brain tissue in patients on a relatively routine basis.

Once tools that allow the assessment of the kinetics of drugs in brain tissue are available for clinical studies, we can rigorously address the question of the relationship between drugtime-concentration curves in the brain and clinical efficacy. Until then, those interested in the development of neurotherapeutics are obligated to consider the BBB (and all other factors) that may limit the access of drugs to the brain. When feasible, investigators should pursue tissue-based studies to assess whether the minimal concentration required for efficacy is achieved using the existing tools. Unfortunately, such assessments are largely limited to patients with conditions that require frequent surgery in the course of their clinical care. For example, in neurooncology, an increasingly common clinical strategy is to (1) systemically define the maximum tolerated dose based on toxicity, (2) assess tissue concentrations at the maximum tolerated dose via direct tissue analysis, and if adequate concentration is achieved, (3) proceed with efficacy testing. Although labor intensive, such an approach provides certainty that any drug that advances to efficacy testing is both

tolerable to the patient and accessible to the site of the disease. Agents that fail to accomplish this should be eliminated from further clinical development for brain diseases. Despite the additional time and resources that this strategy would require upfront, it may paradoxically reduce the time it would take to identify effective therapeutics for brain disease. It is estimated that the current cost of developing 1 drug for clinical use ranges from \$350 million to \$5 billion.⁷ With the ever-increasing cost of clinical trials, it seems prudent to invest some of those dollars in the early investigation of how a drug works inside and outside of the BBB when treating brain disease.

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