Crossing the blood–brain barrier: are we getting it right?

'Future growth in the neuropharmaceutical market is limited by the inability to target drugs through the blood–brain barrier'

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Not one pharmaceutical company in the world today has a molecular blood–brain barrier (BBB) research program. However, such a BBB research program would provide the platform for CNS drug targeting, just as the molecular neurosciences create the platform for CNS drug discovery. Current CNS drug development programs comprise only CNS drug discovery research, without parallel programs in CNS drug delivery or targeting. This imbalance between CNS drug discovery and CNS drug targeting is peculiar, especially considering that more than 80 million individuals in the USA alone have some disorder of the CNS, and yet 98% of all new drugs discovered for such disorders do not cross the BBB. The reasons for this imbalance are two-fold, and arise from priorities existing within both the academic neurosciences and the pharmaceutical industry.

On the academic side, BBB research has been chronically underdeveloped within the molecular neurosciences. For example, the 30th Annual Meeting of the Society for Neuroscience (New Orleans, LA, USA, 4–9 November 2000) devoted approximately 0.1% of abstracts to BBB research. Coincidentally, the volume of the brain capillary endothelial cell, which forms the BBB *in vivo*, is only 0.1% of the total brain volume. Therefore, it could be argued that the small representation of BBB research within the overall neurosciences is proportional to the functional role of the BBB in the brain. However, in fact, the BBB plays a role in virtually every disease process involving the CNS and is a crucial issue in the development of all drugs for the CNS. Because the molecular and cellular biology of the BBB is not a significant part of the neuroscience mission, the number of neuroscientists trained each year in BBB research is minimal. Therefore, even if a large pharmaceutical company wanted to start a BBB drug delivery program, there would be few, if any, BBB trained scientists to hire.

The second reason for the imbalance between CNS drug discovery and drug delivery in the overall CNS drug development process is derived from current thinking within the pharmaceutical industry. It is traditionally believed that small molecules cross the BBB, and so no BBB drug delivery program is required. In fact, most small molecules do not cross the BBB[1], and only small lipophilic molecules of less than 400 Da can traverse the BBB. This assumes that such molecules are neither bound by plasma proteins nor are substrates for the multiple active efflux transport systems at the BBB.

CNS drug discovery processes

Many drugs that were discovered in the old trial-and-error drug discovery process were below the 400 Da threshold, and many were lipid soluble. This process worked. There are many CNS pharmaceuticals in the markets today, and all of these drugs fulfill the dual molecular criteria of lipid solubility and a molecular weight below the 400 Da threshold. By contrast, in 21st century CNS drug discovery, the trial-and-error process has given way to rational drug design, which uses a receptor-based HTS methodology. Small-molecule drug candidates are selected on the basis of their binding to receptors, and therefore will invariably have molecular weights greater than the 400 Da threshold and have significant degrees of hydrogen bonding and low lipid solubility. Therefore, the majority of promising drug candidates that emerge from a HTS program will not cross the BBB. Given the absence of a parallel CNS drug delivery program, then the CNS drug development is terminated. However, if members of the CNS drug discovery and drug targeting teams worked closely together, strategies could be formulated to modify the structure of the drug without compromising drug activity, such that the drug could cross the BBB at pharmacologically active concentrations. This collaboration must occur in the earliest phases of the CNS drug development process.

Large-molecule CNS therapies

There are many approaches to solving the BBB drug targeting problem[2] without resorting to the methods of the past

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that involved drilling holes in patients' heads or infusing noxious agents into the carotid artery to cause BBB disruption. As we begin the 21st century, it should be considered whether or not technologies will be introduced that alter the way CNS pharmaceuticals evolve in the future. In the 20th century, pharmaceutics placed an emphasis on the discovery of small molecules and was a chemistry-driven process[3]. By contrast, in the 21st century, pharmaceutical discovery might be a biology-driven process with increasing importance attached to the discovery of large-molecule pharmaceuticals. The conversion from chemistry-driven small-molecule to biology-driven large-molecule pharmaceutical discovery will be accelerated by the application of the genomics sciences and gene microarrays. Gene discovery, in parallel with the availability of the complete sequence of the human genome, will rapidly lead to the discovery of thousands of new large-molecule drug candidates. Whereas small molecules are essentially palliative medicines, large-molecule pharmaceuticals have the potential to be curative medicines. Can you name a single chronic disease of the brain, or any organ, that has been cured by small-molecule drug therapy? By contrast, large-molecule pharmaceuticals such as gene medicines, antisense drugs, or recombinant proteins have the potential to be curative medicines, or at least symptomatic treatments for chronic disease.

The caveat is that large-molecule pharmaceuticals will not be effective drugs for the brain, or for most other organs, unless these molecules can reach their therapeutic targets within the cell. Large-molecule neuropharmaceuticals cannot be developed in the future without first creating effective BBB drug targeting technologies[2]. The goal of CNS drug targeting research is to create a molecular formulation of the drug that enables transport across any biological barrier. For example, drugs that react with receptors on the plasma membrane must be formulated to undergo transport across the brain microvascular barrier, which forms the BBB *in vivo*. By contrast, drugs such as gene or antisense medicines must be enabled to undergo transport through multiple serial membranes, including the BBB, the target cell plasma membrane, the intracellular endosomal membrane and the nuclear membrane. The circumvention of these biological membranes is difficult, but can be done by merging the diverse technologies that are available within the drug targeting sciences. If the intent is to develop non-invasive, non-viral gene therapeutics for the brain, it might be necessary to combine monoclonal antibody technology, liposome or nanoparticle technology, polyethyleneglycol technology, and molecular biology, as recently described[4]. Non-invasive delivery to the brain of non-viral gene therapeutics is an extreme example, but illustrates the diversity of technologies currently available that can be combined to solve the problem of CNS drug targeting.

Whether the future lies in small molecules or large molecules does not really matter. In either case, CNS drug developers will require access to effective CNS drug targeting strategies. If the targeting technology is not available, then CNS therapies for the future will consist of old-fashioned 20th century lipid-soluble and low molecular weight drugs, which does not bode well for the millions of individuals suffering from chronic diseases of the brain.

References

1 Pardridge, W.M. (1998) CNS drug design based on principles of blood–brain barrier transport. *J. Neurochem.* 70, 1781–1792

2 Pardridge, W.M. *Brain Drug Targeting: The Future of Brain Drug Development*, Cambridge University Press (in press)

3 Drews, J. (2000) Drug discovery: a historical perspective. *Science* 287, 1960–1964

4 Shi, N. and Pardridge, W.M. (2000) Non-invasive gene targeting to the brain. *Proc. Natl. Acad. Sci. U. S. A.* 97, 7567–7572

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