Commentary

Themed Issue: Current Advances in Central Nervous System Delivery of Therapeutic Molecules
Guest Editors: Jean-Michel Scherrmann and Craig K. Svensson

Commentary: Current Advances and Future Directions for CNS Delivery

Craig K. Svensson^{1,3} and Jean-Michel Scherrmann²

Received 7 October, 2008; Accepted 13 October, 2008; Published online 12 December 2008

KEY WORDS: blood–brain barrier; CNS; drug delivery.

Though the central nervous system (CNS) is a common target for drug therapy, over a century of research has demonstrated that access to the CNS is limited by the presence of anatomical barriers that restrict the entry of most xenobiotics. Early attempts to overcome these barriers included direct administration of drugs into brain fluids such as the cerebrospinal fluid of brain ventricles or the interstitial fluid of brain tissue. For obvious reasons, these modes of administration are not easily applicable for chronic delivery and are frequently associated with adverse reactions. For these reasons, CNS delivery across barriers, particularly the blood–brain barrier (BBB), represents a formidable challenge to achieving success in the mitigation of the progression of a growing array of chronic diseases that contribute to substantial morbidity and health care costs in the twenty-first century. For example, pharmacological interventions to stem the increasing burden of Alzheimer's disease and multiple sclerosis will require not only the identification of appropriate targets within the CNS but also strategies to enable complex therapeutics to gain entry at sufficient levels to achieve the desired effect.

Arguably, advances in the *delivery* of therapeutic agents into the CNS will be as important for achieving successful outcomes as will be the identification of appropriate targets and molecules to modulate those targets. Hence, advances in strategies for CNS delivery represent an important area of emphasis for the foreseeable future. With this in mind, we have assembled three reviews focused on advances in CNS delivery by investigators who employ differing strategies to achieve the critical goal of enhancing the delivery of CNS active therapeutic agents. These reviews provide a concise assessment of the state of the art in key approaches to abrogate the anatomical barriers that attenuate achievement of needed concentrations of medicinal agents in the CNS.

CNS delivery strategies have often taken advantage of some unique biological property of the brain microvessel endothelial cells forming the BBB. These unique properties of the brain microvessels *versus* other body vessels could offer the desired organ delivery selectivity. Recent advances arising from transcriptomics and proteomics of the BBB are leading to the discovery of new molecular targets expressed at the BBB for promoting the CNS delivery of chemical or biological medicines. One target area is focused on the transient and controlled opening of the BBB for paracellular delivery. Utilization of this modality will require an understanding of the complete protein network of tight junctions and their signaling pathways. Other target areas are focused on the facilitation of transcellular permeability. This includes the identification of new endogenous transporters which would enable a prodrug approach for the delivery of classical chemical compounds. Additionally, the use of receptors or acceptors expressed at the BBB which engage the transcytosis processes may best be applied to biological medicines.

One key approach to enhancing CNS penetration is to chemically modify agents to provide physicochemical properties that favor CNS entry. As such chemical changes may also alter drug potency, transient modification through the development of a prodrug is an attractive strategy that is carefully reviewed by Rautio and colleagues (1). These authors review three primary strategies for prodrug development: (1) increasing lipophilicity, (2) endowing the molecule with characteristics that enable it to utilize endogenous transporters at the BBB, and (3) antibody- or gene-directed prodrug therapy that permits tissue-targeted release of the active moiety. With the successful introduction of L-dopa over three decades ago, it is perhaps surprising that the prodrug approach has not been more successful in overcoming the barriers to CNS penetration. As discussed by these authors, however, the complexity of this approach is often underappreciated and requires a sophisticated knowledge of CNS anatomy and physiology, as well as the complex chemistry required for success. The opportunities for targeting delivery of prodrugs to the CNS through an antibody- or gene-directed approach are exciting, but as yet untested. However, the potential for optimizing therapy with highly toxic compounds is such that continued effort in this direction merits significant resources.

¹ College of Pharmacy, Nursing, and Health Sciences, Purdue University, West Lafayette, Indiana 47905, USA.

² Université Paris Descartes, Inserm U705; CNRS UMR 7157, Faculté de Pharmacie, 4 avenue de l'Observatoire, 75006, Paris, France.

³ To whom correspondence should be addressed. (e-mail: svensson@purdue.edu)

An alternative to engaging the BBB on a molecular level is to disrupt its barrier properties, thereby providing entry into the CNS of an array of otherwise excluded molecules. David Fortin and his colleagues (2) provide a careful review of the preclinical and clinical data that support the effectiveness of this approach. In addition to discussing experimental data showing that disruption methods do increase CNS permeability, these authors provide a summary of the results of small trials that suggest improved survival when select chemotherapeutic regimens are delivered concurrent with BBB disruption. Though this approach results in a nonspecific increase in the permeability of the BBB, Fortin and colleagues provide a concise summary showing that this intervention is surprisingly well tolerated. Indeed, though long-term neurocognitive deficits are a known consequence of CNS-directed radiation therapy, such deficits are not apparent in patients undergoing BBB disruption. The challenge for this treatment modality is to demonstrate efficacy in a phase III trial that provides sufficient patient numbers to enable a statistically rigorous analysis. Moreover, for this treatment approach to become common practice, data on the variability in degree of disruption with various methods are needed.

While passive diffusion through the transcellular or paracellular routes represents an important means for drug transit across the BBB, the abundance of influx and efflux transporters at the blood–brain interface suggests chemical optimization to enhance or prevent interaction with such transporters to be a logical approach for manipulating CNS delivery of drugs. Numerous reviews of small molecule interactions with such transporters have appeared in the literature. Of particular importance, but receiving less attention, is the employment of transcellular transport processes that enable the passage of large molecules (e.g., proteins) across the BBB. While selective vesicular transport of proteins such as insulin and transferrin have received substantial interest, quantitatively these transport systems are unlikely to provide sufficient movement of therapeutic molecules across the BBB. In their review, Herve *et al.* (3) provide a critical assessment of the utility

of nonspecific adsorptive-mediated transcytosis (AMT). As described by these authors, the capacity for transport is higher in this nonspecific pathway. However, as there is an excess of polyanions surrounding the BBB, cationization of proteins or chemical conjugation with a cationic peptide is necessary to engage AMT as a means of passage across the BBB. As discussed by these authors, important barriers to employment of this strategy persist, such as instability of conjugates, altered action of therapeutic proteins, and potential for immunogenicity. Based upon our present knowledge, a key deficiency in this approach is the lack of specific targeting to the CNS. For this approach to become viable, it is critical to identify distinguishing characteristics of cerebral endothelial cell AMT, as opposed to transport in other endothelial cells. This will allow the development of a more targeted approach to CNS delivery via AMT.

The strengths and weaknesses of the various strategies to enhance CNS drug delivery described in these reviews should convince the reader that a single path will not overcome the obstacles created by the BBB. Exploration of a variety of strategies is critically needed so that the optimal path for specific therapeutic agents can be employed. The various research advances described in this thematic issue provide hope that meaningful therapeutic agents developed for CNS targets will not be abandoned due to our inability to achieve access to the site of action.

REFERENCES

1. J. Rautio, K. Laine, M. Gynther, and J. Savolainen. Prodrug approaches for CNS delivery. *AAPS Journal* **10**:92–102 (2008).
2. M-A. Bellavance, M. Blanchette, and D. Fortin. Recent advances in blood–brain barrier disruption as a CNS delivery strategy. *AAPS Journal* **10**:166–177 (2008).
3. F. Herve, N. Ghinea, and J-M. Scherrmann. CNS delivery via adsorptive transcytosis. *AAPS Journal* (2008). doi:10.1208/s12248-008-9055-2.