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Guest Editorial

The ins and outs of antiviral drug transport in the brain

The study of drug transport in brain has held a unique status, due, in large part, to the specialized barriers (i.e. blood brain barrier, BBB; blood:cerebrospinal fluid barrier, CSF:interstitial fluid barrier) that isolate the brain from the rest of the body. These barriers, for the most part, restrict drug access under normal physiological conditions, and in so doing, lead to bleak consequences for central nervous system (CNS) disease. Pursuant to the realization that drug uptake into brain may be minimal, a swell of methodologies have attempted to quantitate and improve upon these deficiencies. Antiviral and antiretroviral drugs, particularly nucleoside and antisense oligonucleotides, are susceptible to the transport limitations in brain, that has propelled active fields of research on drug design, and delivery. In this issue of the *Journal of NeuroVirology*, Groothuis and Levy (1997) provide a timely and noteworthy assessment of the state of research on the CNS transport of antiviral drugs.

An introductory section succinctly reviews the anatomy and physiology of the brain as it pertains to drug transport, and some of the associated methods of analysis. A key point made by the authors is that brain extracellular fluid (ECF) and cerebrospinal fluid (CSF) drug concentrations should not be assumed equal, due to the distinct, yet heterogeneous, pia-ependyma barrier, as well as due to the diffusional distances a drug must traverse once inside the ECF compartment. As exemplified both through models and experimental data, brain parenchyma drug concentrations are likely to decrease tremendously, and as a function of distance from the pia-ependyma barrier following local drug administration into the CSF.

Two methodological points pertaining to measured brain concentrations warrant comment. First, the authors emphasize the importance of acknowledging the compartmental nature of brain (i.e. vascular, extracellular and intracellular components) and thus, correcting total brain drug concentrations for the vascular contribution is essential. This epitomizes the normal lumping of compartments, integral to methodologically-limited tissue homogenate studies, to attain singular concentration values. Even though the nature of vascular corrections are variable, and species-dependent, it is warranted, particularly for drugs with low BBB diffusivities. Brain microdialysis provides a means to obtain compartment-specific drug concentrations by insertion of a probe into brain extracellular fluid. This method has been applied to a host of drugs in animals with normal brain, and more recently in animals with brain-tumors (Devineni *et al*, 1996). The authors raise a prudent cautionary note of the potential of disrupting the BBB and thus, drug transport, by insertion of the microdialysis probe. Nonetheless, the advantages of microdialysis, including minimizing animal use and intersubject variability, outweigh potential disadvantages and will likely lead to its expanded use. Certainly, drug transport data obtained from microdialysis experiments in the same animal model could be useful to contrast relative transport properties for a series of chemical analogues.

A review of the ability of antiviral and antiretroviral drugs to enter brain indicated that either drugs have very limited access to the brain or further studies are needed to adequately determine brain uptake. Most studies have examined brain disposition of antiviral nucleoside analogs. An analysis of transcapillary exchange of AZT is presented using Equation 7 that predicts that the maximum brain AZT concentration would be 0.01 μg/ml, significantly less than concentrations needed to inhibit HIV-1 replication, and 100-fold less than the model-projected maximum plasma AZT concentrations. It is proposed this is the best case scenario based on their modeling assumptions. Although the overall low propensity for nucleosides to entry brain can be supported, other data have indicated greater brain AZT concentrations and brain:plasma ratios have been attained in various animal models (Brewster *et al*, 1990; Gallo *et al*, 1991). Rather than concentrating only on pharmacokinetic studies designed to quantitate distribution of drug in brain, an extension to develop valid pharmacodynamic models should be initiated. Pharmacodynamic models, relating plasma and brain drug concentrations to viral inhibition and other therapeutic endpoints would serve two functions. One, the influence of viral infection on drug transport could be addressed, and a connection to therapeutic concentrations at least suggested through valid animal models.

The use of a model, such as Equation 7, to predict AZT brain concentrations underscores a potentially powerful tool to characterize antiviral drug disposition in brain. Certainly such models have to be based on measured brain, either total or compartment-specific, drug concentrations, yet the ability to predict, through interspecies extrapolations, human site-specific (i.e. intracellular) concentrations should not be ignored. At the very least, pharmacokinetic

models will allow a distinction between linear and nonlinear or saturable phenomenon that should impact on the design of drug dosage regimens.

An important issue that should be evaluated is the influence of viral disease on antiviral drug disposition in brain. Studies have shown that brain parenchyma viral infections can cause at least transient increases in BBB permeability (Andersen *et al*, 1991; Chaturvedi *et al*, 1991), whereas more chronic alterations in BBB permeability are suggested in individuals infected with HIV-1 (Petito and Cash, 1992). How such alterations impact on antiviral drug BBB transport, or intracellular drug transport and metabolism is unknown, yet studies to determine these relationships are clearly warranted.

Given the less than optimal brain uptake characteristics of antiviral drugs, various drug delivery strategies have been developed and evaluated. It should be appreciated that each type of viral infection affecting brain may have different drug delivery requirements in terms of anatomic target (i.e. glial cells, neurons), and duration of treatment. It is too simplistic an approach to develop systems that increase total brain concentrations without an analysis of site-specific phenomenon that may impact on drug delivery and efficacy. Eradication of chronic infections, such as HIV-1, from the CNS would be enhanced by delivery systems targeted to microglial cells, a primary reservoir of the virus and delivery systems amenable to systemic therapy, preferably an oral dosage form.

In summary, the authors have successfully highlighted the compartmental nature of drug distribution in the CNS, and the limited nature of antiviral drug access to the CNS. Only through comprehensive pharmacokinetic and pharmacodynamic investigations can the disposition of antiviral drugs in brain be characterized. This information will indicate the mechanisms of drug transport, the magnitude of the drug delivery problem, and a viable pathway to advance the design of novel drug delivery systems.

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References

Andersen IH, Marker O, Thomsen AR (1991). Breakdown of blood-brain barrier function in the murine LCMV infection mediated by virus-specific CD8+ T cells. *J Neuroimmunol* **31:** 155–163.

Brewster ME, Anderson W, Bodor N (1990). Brain, blood, and cerebrospinal fluid distribution of a zidovudine chemical delivery system in rabbits. *J Pharm Sci* **80:** 843–846.

Chaturvedi UC, Dhawan R, Khanna M, Mathur A (1991). Breakdown of the blood-brain barrier during dengue infection in mice. *J Gen Virol* **72:** 859–866.

Devineni D, Klein-Szanto A, Gallo JM (1996). *In vivo* microdialysis to characterize drug transport in brain tumors: Analysis of methotrexate uptake in rat glioma-2 (RG-2) bearing rats. *Cancer Chemother Pharmacol* **38:** 499–507.

Gallo JM, Sanzgiri Y, Finco TS, Howarth E, Wilson J, Johnston J, Tackett R, Budsberg SC (1992). Zidovudine serum, cerebrospinal fluid and brain concentrations following chronic administration of a new zidovudine formulation via an implantable pump in dogs. *J Pharm Sci* **81:** 11–15.

Groothuis DR, Levy RM (1997). The entry of antiviral and antiretroviral drugs into the central nervous system. *J NeuroVir* XX.

Petito C, Cash K (1992). Blood-brain barrier abnormalities in AIDS: Immunohistochemical localization of serum proteins in post-mortem brain. *Ann Neurol* **32:** 658–666.