The Applications and The evaluation Methods for the Brain Uptake and Delivery of Candidates of New Drug

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The brain is unique as target for drug delivery because it is an organ with the greatest blood supply, which receives about 20% of the cardiac output in humans and is highly restricted by a tight vascular barrier, the blood-brain barrier (BBB). Since the BBB forms the interface between blood and brain, the biology of the BBB plays a role in multiple disciplines other than pharmacology, physiology, pathology and neurosciences. Despite the important role played by the BBB in so many fields, the number of laboratories worldwide engaged in BBB research is relatively small. Fundamental research in BBB transport processes provides the platform for central nervous system (CNS) drug delivery and CNS drug targeting. It is no coincidence that more than 99% of worldwide CNS drug development is devoted solely to CNS drug discovery, and less than 1% is directed CNS drug delivery. This imbalance between CNS drug discovery and CNS drug delivery can be directly linked to the imbalance in BBB research in the fundamental neurosciences. Also, laboratories specialize in a single technique and fit multiple biological problems to this technique, as opposed to bringing multiple methodologies to bear on a single biological problem. The important questions pertaining to BBB biology are too difficult to address with a single technique, but rather require multidisciplinary approach that employs parallel use of several of the methodologies.

The methodologies needed for examining almost any problem of BBB biology, CNS drug discovery and delivery are presently available, and a parts of methodologies and applications will be discussed in this presentation.

For example, morphine 6-glucuronide (M6G) is said to have special transport properties at the BBB because, despite the high polarity of this compound compared to morphine, the two molecules enter into brain interstitial fluid (ISF) at identical rates based on dialysis fiber measurements. Neuropeptides are said to undergo transport through the BBB in vivo, because the brain volume distribution ($V_o$) exceeds the plasma space in brain ($V_o$) using internal carotid artery perfusion methods. Neuropeptides are said to undergo transport through
the BBB, because $V_o$ is bigger than $V_o$ as measured with the single intravenous injection technique. BBB transport may be studied in tissue culture using an in vitro BBB model, because the brain capillary endothelial cells in culture form a tight barrier compared to cultured human umbilical vein endothelial cells.