Preclinical Prediction of Human Brain Target Site Concentrations: Considerations in Extrapolating to the Clinical Setting

JOOST WESTERHOUT, MEINDERT DANHOF, ELIZABETH C. M. DE LANGE

Department of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, 2300 RA Leiden, the Netherlands

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ABSTRACT: The development of drugs for central nervous system (CNS) disorders has encountered high failure rates. In part, this has been due to the sole focus on blood-brain barrier permeability of drugs, without taking into account all other processes that determine drug concentrations at the brain target site. This review deals with an overview of the processes that determine the drug distribution into and within the CNS, followed by a description of *in vivo* techniques that can be used to provide information on CNS drug distribution. A plea follows for the need for more mechanistic understanding of the mechanisms involved in brain target site distribution, and the condition-dependent contributions of these mechanisms to ultimate drug effect. As future direction, such can be achieved by performing integrative cross-compare designed studies, in which mechanisms are systematically influenced (e.g., inhibition of an efflux transporter or induction of pathological state). With the use of advanced mathematical modeling procedures, we may dissect contributions of individual mechanisms in animals as links to the human situation. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3577–3593, 2011

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INTRODUCTION

Central nervous system (CNS) disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, schizophrenia, migraine, insomnia, depression, and attention-deficit hyperactivity disorder are currently estimated to affect hundreds of millions of people worldwide.[1] Although established treatments are currently available for most of these disorders, significant unmet medical needs still remain, as currently available drugs are treating symptoms rather than curing the disease.[2] Therefore, novel treatments or drugs with a different mechanism of action are needed.

In these days, the CNS sector is struggling as the average cost of getting a drug onto the market is ever increasing and now approaching US$1 billion, whereas there is an expected decline in income due to pricing pressure from generics.[2] Moreover, many potentially therapeutic compounds fail during development because early drug discovery programs are often using the wrong parameters for estimating CNS exposure.[3]

It is often said that many CNS drug candidates fail because they do not reach the CNS target due to lack of blood–brain barrier (BBB) permeability. Indeed, the BBB effectively isolates the brain from the blood by the presence of tight junction proteins, connecting the endothelial cells of the brain vessels. In addition, specific metabolizing enzymes and efflux pumps, such as P-glycoprotein (P-gp), are located within the endothelial cells, which may actively remove drugs from the brain. It is therefore true that the BBB can play a major role in limiting the delivery of systemically administered drugs to the CNS. However, this is not the sole reason for the high failure rate in CNS drug development. For a proper CNS effect, the unbound drug should have the ability to access the relevant target site within the CNS. Apart from BBB permeability, this also depends upon other factors such as plasma pharmacokinetics (PK) and within-brain distribution. These factors are controlled by many

Correspondence to: Elizabeth C. M. de Lange (Telephone: +31-71-5276330; Fax: +31-71-5276292; E-mail: l.lange@lacdr.leidenuniv.nl)

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mechanisms. Each mechanism has its particular influence by its specific rate and extent, and thereby plays a more or less important role in having the drug in the right place, at the right time, and at the right concentration. Moreover, influences of variables such as genetics, gender, age, environmental, and pathological conditions have generally been neglected. It is therefore not surprising that most CNS drug candidates finally fail during development.

As the driving force of CNS drug action is the concentration–time profile at the brain target site, it is important for pharmaceutical companies to have effective and cost-efficient tools to measure and predict human brain target site exposure before proceeding to more expensive clinical trials.

For many (potential) CNS drugs, brain target site concentrations are closely linked, or may even be equal, to unbound drug concentrations in the brain extracellular fluid (ECF).[4,5] However, the possibility of direct measurement of brain ECF concentrations is highly limited in the clinical phase of drug development. Therefore, unbound drug concentrations in human cerebrospinal fluid (CSF) are used as a surrogate for human brain ECF concentrations. However, the usefulness of CSF concentrations as a predictor of brain target site concentrations can be questioned, as a generally applicable relationship between CSF concentrations and brain ECF concentrations does not exist due to qualitative and quantitative differences in processes that govern the PK at these sites.[6–8]

FACTORS THAT GOVERN THE PK IN THE BRAIN

Drug distribution into the brain is governed by many processes, including plasma PK, plasma protein binding, passive and active transport across the BBB or blood–CSF barrier (BCSFB), and once within the brain, bulk flow, diffusion, and passive and active extracellular–intracellular exchange.

Plasma PK and Protein Binding

Once the drugs are in the systemic circulation, they can bind to different proteins that are present in plasma. Of the many plasma proteins that can interact with drugs, the most important ones are human serum albumin, α_1-acid glycoprotein, and lipoproteins.[9] Acidic and neutral drugs are usually bound more extensively to albumin, whereas basic drugs are usually bound more extensively to α_1-acid glycoprotein and lipoproteins.[9] As protein-bound drugs cannot cross the BBB or BCSFB, unbound plasma concentrations, rather than total plasma concentrations, are considered to be the main determinant for the rate and extent of drug entry into the brain.[10] However, it must be noted that information about the level of protein binding by itself is not sufficient for predicting drug distribution into the brain.[11] As the association and dissociation of drugs to plasma proteins is a dynamic process, it indicates that extensively protein-bound drugs can still enter the brain in sufficient amounts, provided that the rate of dissociation and permeability of the BBB and BCSFB is high enough.[12–14] This implicates that information on the kinetics of plasma protein binding is also essential for accurate prediction of the rate and extent of drug entry into the brain.

Transport Across the Blood–Brain Barriers

The barriers between blood and brain are the BBB and the BCSFB. These barriers not only have many similarities but also important differences, as will be discussed below.

The Blood–Brain Barrier

The BBB is formed by the brain capillary endothelial cells, which are interconnected by tight junction proteins that restrict paracellular diffusion of small hydrophilic molecules from blood to the brain. In addition to these tight junctions, numerous active transport systems are present at the BBB that protect the brain from neurotoxic substances, but also help to maintain the homeostasis of the brain by influx of essential substrates such as electrolytes, nucleosides, amino acids, and glucose. These processes are regulated by interactions with adjacent pericytes, astrocytes, and neuronal cells.[15–17] However, in certain specialized regions in the brain, comprising the choroid plexuses and the circumventricular organs, the capillary endothelial cells are fenestrated and therefore highly permeable.[18] Thus, compounds can cross the capillary walls more or less freely in these specialized regions, but may be restricted in entering the rest of the brain by the BCSFB.

The Blood–Cerebrospinal Fluid Barrier

The BCSFB is located at the choroid plexuses in the lateral, third, and fourth ventricles of the brain, which are responsible for the production of CSF. The barrier function of the BCSFB is provided by the tight junctions between the epithelial cells of the choroid plexus at the apical site, which contacts the CSF. Like the BBB, several different active transport systems are located at the BCSFB to limit the entrance into the brain of compounds that can easily permeate the choroid plexus' capillaries.[15,19]

BBB Versus BCSFB

It has been assumed that the surface area of the BBB in humans, which is estimated to be approximately 20 m^2,[20] is at least a 100-fold larger than that of the BCSFB, which is reported to be only 0.2 m^2.[21] This implicates that the BCSFB only plays a minor role in the control of the brain environment.[3,22–24] However, this calculation ignores the large surface