QSAR Analysis of Blood–Brain Distribution: The Influence of Plasma and Brain Tissue Binding

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Received 14 September 2010; revised 11 November 2010; accepted 16 November 2010

Published online 26 January 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22442

ABSTRACT: The extent of brain delivery expressed as steady-state brain/blood distribution ratio (log *BB*) is the most frequently used parameter for characterizing central nervous system exposure of drugs and drug candidates. The aim of the current study was to propose a physicochemical QSAR model for log *BB* prediction. Model development involved the following steps: (i) A data set consisting of 470 experimental log *BB* values determined in rodents was compiled and verified to ensure that selected data represented drug disposition governed by passive diffusion across blood–brain barrier. (ii) Available log *BB* values were corrected for unbound fraction in plasma to separate the influence of drug binding to brain and plasma constituents. (iii) The resulting ratios of total brain to unbound plasma concentrations reflecting brain tissue binding were described by a nonlinear ionization-specific model in terms of octanol/water log *P* and pK_a. The results of internal and external validation demonstrated good predictive power of the obtained model as both log *BB* and brain tissue binding strength were predicted with residual mean square error of 0.4 log units. The statistical parameters were similar among training and validation sets, indicating that the model is not likely to be overfitted. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:2147–2160, 2011

Keywords: QSAR; in silico modeling; nonlinear regression; computational ADME; blood–brain barrier; CNS; passive diffusion; drug transport; plasma protein binding; tissue binding

INTRODUCTION

Brain tissue is separated from systemic circulation by one of the most effective physiological barriers—the blood–brain barrier (BBB).[1] BBB is a complex biological formation consisting of a dense network of tight junctions interconnecting adjacent brain capillary endothelial cells, a variety of metabolic enzymes, and carrier proteins.[1,2] BBB maintains brain homeostasis, limits brain entry of various endogenous compounds, and protects it from xenobiotics.[3] Because of pronounced barrier properties of cerebral vasculature, designing of new central nervous system (CNS) drugs remains a challenging task with the attrition rate among potential neurotherapeutics being higher than in any other therapeutic area.[4] Brain penetration is of great importance not only for CNS-targeted pharmaceuticals but also for peripheral drug candidates as in this case permeable compounds can cause side effects in brain.[5] Estimation of brain delivery potential of candidate compounds is desirable at the earliest stages of drug discovery.

Steady-state blood to brain distribution ratio (expressed as log *BB* constant) has been traditionally used as a quantitative measure of brain penetration. The prevalence of this parameter can be attributed to the fact that it is understandable for a medicinal chemist and easier to measure compared to kinetic

Abbreviations used: BBB, blood–brain barrier; CNS, central nervous system; $D_{o/w}$, pH-dependent octanol/water partitioning coefficient; $f_{u,br}$, unbound fraction in brain; $f_{u,pl}$, unbound fraction in plasma; $K_{b,app}$, apparent brain tissue binding constant; log *BB*, logarithm of brain/blood distribution ratio of a solute; log *PS*, logarithm of permeability-surface area product of a solute; MAE, mean absolute error; MW, molecular weight; *N*, number of compounds; N_{HA}, number of H-bond acceptors; N_{HD}, number of H-bond donors; N_{RB}, number of rotatable bonds; $P_{o/w}$, octanol/water partitioning coefficient of neutral species; pK_a, acidic ionization constant; %PPB, percentage plasma protein binding; p($S_{P\text{-}gp}$), probability of the compound being a P-gp substrate; RMSE, residual mean square error; TPSA, topological polar surface area; V_x, McGowan characteristic volume.

Additional Supporting Information may be found in the online version of this article. Supporting Information

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Journal of Pharmaceutical Sciences, Vol. 100, 2147–2160 (2011)
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BBB permeability data (log *PS*).[2] Several authors noted that a drug may be considered CNS permeable if its log *BB* value exceeds certain threshold (the optimal threshold for classification is typically specified between 0 and –1).[6–11] However, using log *BB* as a sole determinant of brain penetration may result in misleading conclusions. Low value of this parameter is often simply an indication of extensive plasma protein binding, whereas unbound molecules may readily cross BBB and exhibit central action (e.g., ibuprofen[7] and midazolam[12] are both centrally acting drugs having log $BB < 0$ due to high protein binding in plasma). This example illustrates the importance of the correct interpretation of brain transport characteristics. It is the low rate of passive diffusion across BBB (log *PS* constant) rather than the low brain/plasma partition ratio that allows identifying compounds unable to enter the brain due to poor membrane permeation.[13] Instead, log *BB* provides an insight on the actual extent of brain delivery at steady-state conditions. Both parameters are needed for a comprehensive evaluation of blood–brain transport potential of new compounds, and any single property would not suffice to guide decision making in drug discovery.

Numerous attempts to predict drug partitioning between brain and plasma using *in silico* methods had been reported up to date. For an outline of the most notable earlier works, one can refer to Refs. [14–16] or a more recent review[17]; however, a brief summary of several studies published in the past few years is presented in Table 1. Proposed models vary significantly in terms of methodological approaches ranging from simple regression equations describing log *BB* as a linear combination of selected physicochemical properties to complex models utilizing sophisticated statistical techniques and large pools of theoretical descriptors. Yet, some drawbacks are frequently noted in these models. First, the number of data points used to parameterize the models is typically small, and little effort is being made to ensure that only high-quality data are used for modeling. A common approach is to collect the data from several previously published data sets without raising any concerns regarding the possible involvement of different BBB transport mechanisms or performing any other verification procedures. Second, the obtained log *BB* values are usually fitted "as is" disregarding the complex nature of this parameter and its relationship with plasma protein binding. Only one of the presented modeling approaches[18] accounts for both fraction unbound in plasma and probability of P-gp mediated efflux, albeit by simply including these properties among the descriptors in the artificial neural network model. The respective model is also likely to be over-fitted because reported residual mean square error (RMSE) values are smaller than the error of experimental log *BB* determination, which is at least 0.3 log units.[7,14] In general, if the performance of the models summarized in Table 1 is considered, it can be noted that most of the authors report very good prediction errors (expressed as RMSE or mean absolute error), but the overall correlation between experimental and observed log *BB* varies considerably with R^2 values spanning the range from about 0.5 to 0.9. Better R^2 is usually obtained when the data set used for modeling includes a significant amount of very large or very small log *BB* values disregarding the fact that extreme data points may not adequately reflect passive equilibration across BBB as they might be affected by carrier-mediated transport or other issues. Finally, the majority of above-mentioned models except the most recent work by Fan and coworkers[8] were not tested on an external validation set and their actual predictive power remains highly questionable.

Recent publications showed increased attention to the fact that only unbound drug molecules may be responsible for its pharmacological efficacy, and the paradigm has shifted toward evaluating both rate and extent of brain penetration as well as brain tissue binding affinity of drugs instead of focusing on a single property.[19–22] In a recent review, Reichel[23] pointed out that the evolving concept of "CNS pharmacokinetics" that requires estimating a variety of interrelated brain transport characteristics can make the majority of existing QSAR models focusing on the prediction of a single log *BB* parameter obsolete. Under these circumstances, any new log *BB* model should maintain a theoretical relationship with underlying properties, namely plasma and tissue binding.

Despite the fact that significance of brain tissue binding is now widely recognized, very few attempts have been reported up to date to predict this property. Wan et al.[24] experimentally determined unbound fractions in brain for 108 CNS active molecules (including 83 proprietary compounds) and analyzed their relationship with octanol/water log *P* and other descriptors representing molecular structure. Because brain tissue binding is mainly governed by lipophilicity, a simple correlation with log $P_{o/w}$ yielded RMSE about 0.5 log units, which was further improved by inclusion of additional descriptors. In a more recent study,[25] the same authors correlated $f_{u,br}$ with microemulsion retention factors (log k'_{MEEKC}). This approach led to even better results, but it requires experimental measurement of log k'_{MEEKC} values and is not suitable for the analysis of virtual compound libraries. Another notable series of publications by Rodgers and coworkers[26–28] deals with predicting tissue to plasma partitioning coefficients corrected for plasma protein binding. In these studies, PBPK (physiologically based pharmacokinetic) modeling approach is employed instead of conven-

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