Classification of Drugs by CNS Access: An Insight from Quantitative Blood-Brain Transport Characteristics

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INTRODUCTION

The ultimate goal of QSAR analysis focusing on blood-brain barrier penetration is the ability to discriminate between CNS active and inactive molecules. The objective of the current study was to establish the relationship between quantitative blood-brain transport parameters and qualitative data indicating whether the compound penetrates into the brain efficiently enough to exhibit action in the central nervous system (CNS). Two quantitative characteristics were considered: brain/plasma equilibration rate (log [$PS \cdot f_{u,br}$]), and the extent of brain/plasma partitioning at equilibrium (log *BB*). Analysis of a diverse data set consisting of >1500 compounds from the World Drug Index (WDI) database with experimentally assigned brain penetration categories revealed that a linear combination of the above mentioned parameters allowed classification of drugs by CNS access with 94% accuracy. Furthermore, the devised classification score correlated well with the unbound brain/plasma partitioning coefficient (log $K_{p,uu}$), which is recognized as an unambiguous determinant of brain exposure. The obtained results confirm the validity of the proposed classification approach.

EXPERIMENTAL DATA & QUANTITATIVE PARAMETERS

Binary classification—data was taken from the study by Adenot & Lahana[1]. The data set consisted of 1696 molecules from the WDI database with all neurotherapeutics classified BBB positive, and molecules known to be restricted from brain entry BBB negative. 81 BBB negative compounds flagged as P-gp efflux substrates, and 25 amino-acids or other BBB positive molecules subject to carrier-mediated influx were excluded, leaving us with a final set of 1581 molecules.

Brain exposure—data was represented by $K_{p,uu}$ – the unbound brain/plasma partitioning coefficient. The current study employed a data set reported by Fridén et al., that contained *in vivo* $K_{p,uu}$ for 41 compounds measured in rats using the brain slice method[2].

The following quantitative characteristics of BBB transport were considered when deriving classifications:

•**Rate of brain penetration:** log*PS* – logarithm of **P**ermeability-**S**urface area product. Calculated using a non-linear ionization-specific model based on 178 compounds that cross BBB by passive diffusion. Full details of model development can be found in reference 3[3].

•**Extent of brain penetration:** log*BB* – logarithm of **B**rain/**B**lood partitioning ratio at steady-state. Calculated on the basis of the ratio $f_{u,pl}/f_{u,br}$ that is equal to *BB* for passively distributing molecules. The extent of plasma binding ($f_{u,pl}$) was estimated using the algorithm implemented in ACD/Percepta while a physicochemical brain tissue binding model ($f_{u,br}$) for 470 molecules, was derived similarly to log *PS*[4].

•**Brain/plasma equilibration rate:** log ($PS \cdot f_{u,br}$)**.** Liu et al.[5] have shown that equilibration time between brain and plasma may be quantified using a term named intrinsic equilibration half-life ($t_{1/2eq,\,in}$). The inverse of time can be viewed as an equilibration rate, which, after omission of constant terms, is given by a product of permeability (*PS*) and unbound fraction in brain.

BBB SCORE & CLASSIFICATION ACCURACY

Classification of drugs by their accessibility to CNS relies on the devised BBB permeation score (S_{BBB}), which is defined as a logarithm of the product of brain/plasma equilibration rate and the extent of penetration when this equilibrium is achieved:

$$S_{BBB} = \log(PS \cdot f_{u,br}) + \log BB = \log\left(PS \cdot \cancel{f_{u,br}} \cdot \frac{f_{u,pl}}{\cancel{f_{u,br}}}\right) = \log(PS \cdot f_{u,pl})$$

Since the $f_{u,br}$ terms cancel out in the above expression, a BBB score can be seen as a representation of *in vivo* BBB permeability, i.e. intrinsic *PS* corrected for plasma protein binding.

In a preliminary study[6], we have demonstrated that a combination of the respective quantitative parameters leads to uneven distribution of data points belonging to BBB+ and BBB– subsets (Fig. 1). A Linear Discriminant Analysis (LDA) procedure applied to the final data set revealed that the optimal cut-off is S_{BBB} = -3.5 (Fig. 2, A), the overall accuracy of classification is 94.5%, and Wilk's statistic: U = 0.70.

Observed class	Predicted class		Statistical characteristics	
	BBB+	BBB–		
BBB+	1239	72	Sensitivity	94.5%
BBB–	26	244	Specificity	90.4%
	97.9%	77.2%	Accuracy	93.8%

TABLE 1. Contingency table of drug classification by CNS access.

NOTE: Higher sensitivity compared to specificity reflects the nature of experimental data. A certain amount of false positives could arise due to the fact that the classifier can only estimate if the molecule penetrates into the brain sufficiently for central effect to occur, but not if it will indeed be active once it enters the brain.

ONSET & DURATION OF ACTION

As shown previously, the definition of BBB score can be simplified to one composite descriptor, and knowledge of log*BB* values is not strictly required for classification. In spite of this, separating the contributions of kinetic and thermodynamic components and visualizing the data on a two-dimensional scale, as demonstrated in Fig.1, provides useful insights into the pharmacokinetics of the drug. For CNS drugs, the individual parameters roughly reflect their onset and duration of action:

1. **Tricyclic antidepressants** (green) are usually characterized by very long duration of action (up to several days). Almost all drugs of this class concentrate in the upper part of the plot with log*BB* > 0.
2. **Benzodiazepines** (blue) vary by duration of action from ultra-short to long acting, typically with more rapid onset. This is well reflected by estimated BBB parameters as this drug class is shifted towards higher brain/plasma equilibration rates while spanning a wide range of log*BB* values.
3. **Inhalational anesthetics** (purple) provide an example of a drug class of extremely rapid onset of action. These are usually small molecules highly permeable across BBB, yet having a considerable unbound fraction in brain. As a result, they achieve equilibrium very rapidly.

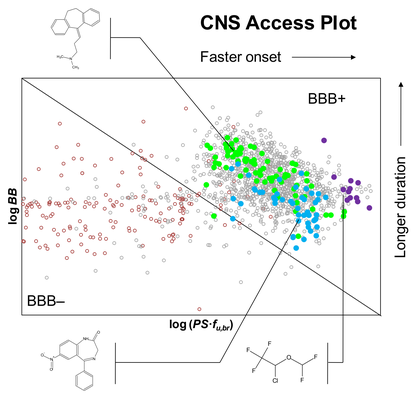

FIGURE 1. CNS Access Plot with colored point swarms representing specific drug classes.

BRAIN EXPOSURE

$K_{p,uu}$ as a measure of brain exposure primarily reflects the transport mechanism, and a value close to 1, independent of drug's physicochemical properties is generally presumed for passively diffusing molecules. Nevertheless, even in the absence of carrier-mediated processes, apparent $K_{p,uu}$ may still be less than unity if the respective molecule is not permeable enough to reach steady-state conditions. In this case, a direct relationship between permeability and brain exposure should be expected.

Fig. 2, (B) illustrates the correlation between experimental log $K_{p,uu}$ and estimated *in vivo* BBB permeability represented by BBB scores. Apparently, S_{BBB} is highly predictive of brain exposure, and when experimentally assigned categories[4] are marked by green and red dots, the $K_{p,uu}$ threshold separating the two classes becomes evident (indicated by dashed line). It can be concluded that 10% free drug exposure to brain is enough for the compound to be designated BBB positive. This is fully consistent with reported cut-off values[7], and our classifier correctly recognizes 103 of 111 (93%) CNS drugs from the benchmark set presented therein.

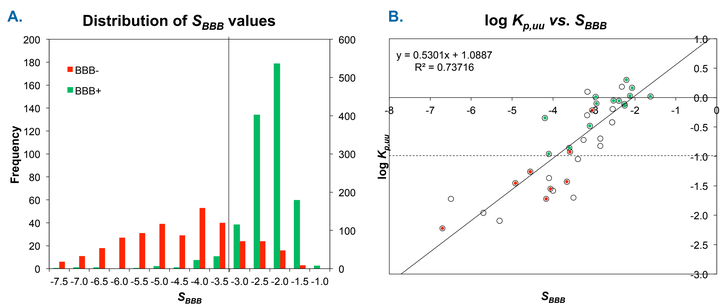

FIGURE 2. **(A)** Discrimination of BBB+ and BBB– classes by CNS scores (S_{BBB}); **(B)** Correlation between these scores and brain exposure given by K_p^{uu}.

SOFTWARE FOR DRUG CLASSIFICATION BY CNS ACCESS

The described algorithms for calculating quantitative blood-brain transport parameters and classifying drugs by CNS access are available on the ACD/Percepta software platform:

1. BBB module

Provides a unified interface for all BBB-related predictions, and offers the following output:

- **Calculated values** of log*PS*, log*BB* and brain/plasma equilibration rate with traffic lights showing whether the values are favorable or unfavorable for efficient brain delivery
- Estimated **Classification**
- **Scatter plot** displaying the position of the analyzed compound compared to a selection of known drugs
- **Alerts** (if applicable) indicating the possible presence of carrier-mediated influx or P-gp efflux
- **Physicochemical descriptors** used in the calculation with the capability to enter more precise values, or simulate how changing inputs would affect BBB transport

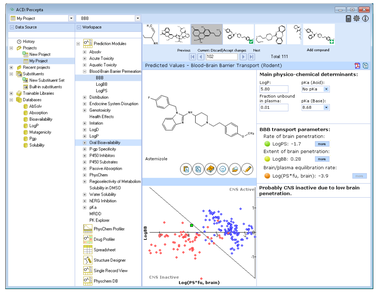

FIGURE 3. ACD/Percepta BBB module.

2. LogBB & LogPS modules

Dedicated modules providing additional details about the calculation of a particular property:

- **LogBB** module provides calculated brain tissue binding in terms of fraction unbound in brain ($f_{u,br}$)
- **LogPS** module includes more detailed simulation capabilities including hydrogen bonding and molecular size contributions
- Both modules present up to 3 of the most similar compounds from the training sets, used to derive the models

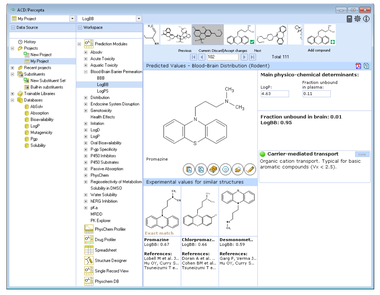

FIGURE 4. ACD/Percepta LogBB module.

3. Categorizing & Ranking

In addition to the aforementioned Prediction modules, ACD/Percepta includes advanced functionality for simultaneous analysis of multiple molecules:

- **Spreadsheet Workspace** offers powerful batch calculation capabilities where entire compound libraries can be automatically classified and ranked according to CNS access and a variety of other ADME-Tox properties.
- **Drug Profiler** module enables easy interpretation of results through color-coded, user-defined property thresholds to indicate different classifications, and enables reversal of the target score (i.e. the capability to select if the drug is centrally acting or peripheral).

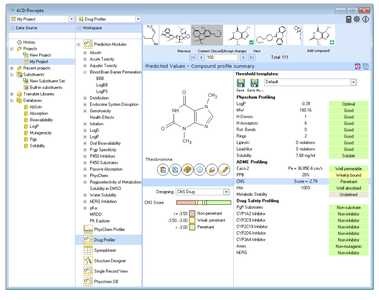

FIGURE 5. CNS Categories in ACD/Percepta Drug Profiler module.

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