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Prediction of blood–brain barrier penetration: are we missing the point?

Over the past 15 years, many models for the prediction of blood–brain barrier penetration have been reported and comprehensively reviewed [1], including a recent review in *Drug Discovery Today* [2]. A common feature of all these models is the prediction of total (i.e. bound + free) drug concentration in the brain, usually expressed as the log of the brain:blood (or plasma) ratio. One issue that does not seem to have been addressed is if these predictions of total drug concentration are relevant to pharmacological action.

Expanding on the work of Kelder [3], literature data on the brain penetration of >100 clinically-used drugs were compiled and plotted against the calculated polar surface area (PSA), which is a measure of the hydrogen bonding capability of the drug. Although the dataset was inherently variable (encompassing different species, dosing regimens, sampling times, blood or plasma), the observed trend of increasing brain:blood ratio with decreasing PSA was consistent with the role of hydrogen bonding as described by other groups [1,2]. Drugs that are known to be substrates for efflux transporters generally have lower ratios than would be predicted from PSA. From this rather simple model, and from more advanced models [1,2], we would appear to be in a good position to predict (at least semi-quantitatively) the *in vivo* activity of drugs in the brain – or are we?

It has been stated that brain penetration data based on total drug concentration 'reflects nothing but an inert partitioning process of drug into lipid material' [4]. If this is indeed the case, it is perhaps not surprising that good predictive models have been developed. But have we really achieved anything useful? The majority of CNS receptors to which drugs are targeted are G-protein-coupled receptors (GPCRs), including the dopamine, 5-hydroxytryptamine, opiate, purine and benzodiazepine receptors. Given that the ligand-binding domain of GPCRs is thought to be in contact with extracellular fluid (ECF), it has been suggested that brain-ECF (bECF) drug concentrations (essentially free drug), provide the most relevant link with pharmacological action [5]. As a more-easily obtainable alternative, cerebrospinal fluid (CSF) concentrations (again, essentially free drug) could provide a surrogate for bECF because, at distribution equilibrium, free drug concentrations will be the same throughout the body (with a number of caveats [5,6]).

With this in mind, literature data on CSF and free plasma concentrations of >70 clinically-used drugs were compiled. Approximately 70% of these drugs have a PSA <60 $Å^2$ and (with the exception of efflux transporter substrates) the vast majority of these exhibit a CSF: free plasma ratio approximating to unity. Direct comparisons of drug levels in brain, CSF and plasma in the same reports are scarce. However, these datasets suggest that despite large variations in the concentration ratios of total drug, the levels of free drug in the brain are in equilibrium with the plasma compartment.

What about pharmacological action? Literature reports linking drug concentration with effects in the CNS seem to point to the importance of free drug concentration. For example, in a study of anesthetic action, phenobarbital was infused in rats at five different rates [7]. Plasma and brain concentrations of phenobarbital at the onset of anesthesia (loss of righting reflex) were found to increase with increasing infusion rate. However, the CSF concentration of phenobarbital at the onset of anesthesia was found to be the same for all infusion rates, indicating that the CSF was in close equilibrium with the effect compartment. A similar design was used to investigate the pharmacokinetics and pharmacodynamics of theophylline with respect to seizures [8]; again, CSF was found to be predictive of pharmacological activity. The time course and magnitude of the pharmacodynamic effect of 1,4-substituted benzodiazepines has been shown to correlate with CSF and free plasma concentrations [9,10].

Experimental determination of total drug concentrations in the brain and blood could well provide useful information on, for example, the time course of drug action or the importance of efflux transporters. However, to predict the brain:blood

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ratio of total drug concentration would appear to be of limited value unless, for the receptor in question, total drug levels have been shown to be relevant. In the absence of this link, literature evidence suggests: (i) the importance of considering free drug concentrations in the brain; (ii) that the equilibrium theory of free drug applies to the 'CNS compartment'; and (iii) the potential use of CSF drug concentrations as a surrogate for free drug concentration in the brain.

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Stacking up the armory against viruses

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The recent *Future Antivirals: Latest Developments in HIV, Hepatitis, Herpes, Influenza, RSV & SARS* conference (12–13 November 2003, London, UK) focussed on the major advances and novel solutions in the field of antiviral drug development. At present, antiviral R&D programs are concentrating on the development of drugs designed to inhibit the action of viral proteins, but there is increasing evidence that host cells will also afford important targets for therapeutic agents [1,2]. Antivirals that exploit the host response already exist, for example, interferon-α (IFN-α). Although there are chemotherapies available for the treatment of influenza, herpes simplex, varicella–zooster, cytomegalovirus, respiratory syncytial virus (RSV), papilloma, hepatitis B, hepatitis C and HIV infections, there is still a significant unmet medical need for novel drugs to combat these diseases. Perhaps of greater concern is the need for drugs to treat newly emerging infections, for example Severe Acute Respiratory Syndrome (SARS) and West Nile Virus (WNV).

Emerging viral infections

In terms of emerging diseases, an interesting outlook was presented by Paul Kellam (University College of London; http://www.ucl.ac.uk). As a result of the continuing improvement in molecular and biochemical technologies, the number of viruses and associated infections that can be detected is constantly increasing, as illustrated by the recent SARS outbreak. SARS-CoV was unambiguously identified in November 2002. In April 2003, the link between SARS-CoV and the disease was established, and in May 2003 the full genome was sequenced. Meanwhile, Pfizer (http://www.pfizer.com/main.html) launched a drug development program on the SARS-CoV 3CL protease. Wade Blair (Pfizer) reported on anti-SARS-CoV compounds that show activity in an *in vitro* retroviral assay. Pfizer pursued homology modeling of the SARS-CoV 3CL protease, based on the human rhinovirus 3C protease (HRV-2 3C protease) crystal structure, and their current lead out of this program is

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