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Molecular Factors Influencing Drug Transfer across the Blood–Brain Barrier

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Abstract

A recently reported approach to the prediction of blood–brain drug distribution uses the general linear free energy equation to correlate equilibrium blood–brain solute distributions (logBB) with five solute descriptors: R_2 an excess molar refraction term; π_2^H, solute dipolarity or polarizability; α_2^H and β_2^H, the hydrogen bond acidity or basicity, and V_X, the solute McGowan volume. In this study we examine whether the model can be used to analyse kinetic transfer rates across the blood–brain barrier in the rat.

The permeability (logPS) of the blood–brain barrier to a chemically diverse series of compounds was measured using a short duration vascular perfusion method. LogPS data were correlated with calculated solute descriptors, and octanol–water partition coefficients ($logP_{oct}$) for comparison.

It is shown that a general linear free energy equation can be constructed to predict and interpret logPS values. The utility of this model over other physicochemical descriptors for interpreting logPS and logBB values is discussed.

Optimum delivery of therapeutic drugs to the brain is hindered by the presence of the blood–brain barrier which tightly controls the exchange of substances between the blood and the central nervous system (CNS). The blood–brain barrier is formed by high-resistance tight junctions (zonulae occludentes) between adjacent endothelial cells in the cerebral micro-vessel walls (Reese & Karnovsky 1967) and between the epithelial cells of the chord plexus. The micro vessels form the principal route by which drugs enter the brain, making up 95% of the total surface area of the blood–brain barrier (Smith 1989). The absence of an intercellular transport route across these vessels, combined with a lack of transcellular water-filled channels or fenestrations (Brightman & Reese 1969), gives rise to a capillary network that behaves as an extended cell membrane. Therefore, to pass into the brain solutes must take the transcellular route, which involves either passive diffusion or transport via a specific carrier, as occurs for essential brain nutrients, including glucose and amino acids (Pardridge 1983). The blood–brain barrier also possesses active-efflux mechanisms for certain classes of drug (Ghersiegea et al 1994). Net rate of uptake into the brain for these drugs will be dependent upon the rate of brain-to-blood efflux and on the blood-to-brain permeation rate.

Terms such as 'brain penetration' or 'the ability of drugs to cross the blood–brain barrier' are widely used in the pharmaceutical literature, often without any definition of the means of measurement of brain penetration or of the ability to cross the blood–brain barrier. Because for most solutes passage through the blood–brain barrier is rate-limiting (Bradbury 1979) and can be equated with the micro-vessel wall, it is logical to consider two parameters of brain uptake. The first is the permeability of the micro-vessel wall or blood–brain barrier to a drug and the second the steady-state distribution of the drug between brain and blood (or blood plasma). The permeability has generally been estimated by relating the brain uptake of a radiolabelled drug to its concentration in plasma or in a perfused physiological saline during short-term exposure. If a value of the surface-area of brain micro-vessels per unit weight of brain is assumed, a permeability coefficient with dimensions of length $\times$ time^{-1} can be calculated. More commonly, surface area is subsumed into a composite constant, the permeability-surface area (PS) product (Renkin 1959), with dimensions of length^3 $\times$ time^{-1} $\times$ weight^{-1}.

Although Krogh (1946) pointed to lipid solubility as being the prime determinant of brain entry, Mayer et al (1959) seem to have been the first to relate a rate constant for entry into the cerebrospinal fluid (CSF) or brain to the partition coefficient, P, of a compound between heptane, benzene or chloroform and water. Later, no doubt on the basis of the work of Hansch et al (1968), the octanol–water log P was used to predict penetration of iodinated organic acids into the brain (Rapoport & Levitan 1974). Subsequent studies of the permeability of the blood–brain barrier have generally related this parameter to P_{oct} or to this property divided by the square root of molecular weight (MW) (reviewed by Fenstermacher & Rapoport 1984). Although the regression of the PS-product for 16 simple compounds against $P_{oct} \times MW^{-1/2}$ was linear over four orders of magnitude of $P_{oct} \times MW^{-1/2}$, the observed values of the PS-product occasionally differed from those predicted and the difference could be as much as an order of magnitude.

Levin (1980) determined blood-plasma-to-brain permeability coefficients, P_c, in rats and correlated the $logP_c$ values with a function of $logP_{oct}$ and drug molecular weight, MW, i.e. log $[P_{oct} \times (MW)^{-1/2}]$. For 22 drugs he obtained $\rho = 0{\cdot}91$; we denote the number of datapoints as n, the correlation coefficient as ρ, the regression standard deviation as s.d., and the

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F-statistic as F. Subsequently (Hansch et al 1987) use of a regression against $\log P_{oct}$ and logMW as independent variables yielded a regression with n = 23, $\rho = 0{\cdot}927$ and s.d. = 0·46 log units. Pardridge et al (1990) obtained the permeability-surface area product, PS, for 17 drugs, this time from physiological saline to the brain. A regression of log $[PS \times (MW)^{-1/2}]$ against $\log P_{oct}$ was shown to have $\rho = 0{\cdot}84$ for 13 of the drugs.

More recently Chikhale et al (1994, 1995) have used the rat-brain perfusion technique to obtain permeability coefficients from physiological saline for a series of model peptides. They then compared the $\log P_c$ values for seven model peptides with various solvent partition coefficients and found ρ values of 0·598 against $\log P_{oct}$, of 0·874 against the $\Delta\log P$ parameter of Seiler (1974) and of 0·970 against logP for partition between ethylene glycol and heptane. Chikhale et al (1994, 1995) concluded that a main determining factor was the amide 'hydrogen bonding potential', although it is not clear if this refers to the ability of the amides to act as hydrogen-bond acids, hydrogen bond bases, or both.

The second parameter, the blood–brain distribution at or near the steady-state is more difficult to obtain, but has been measured by Young et al (1988). In such studies, factors other than capillary permeability influence the final concentration of drug in the brain. If it is assumed that there is no active transport in either direction across the capillary wall, these factors include solubility and binding of the drug in brain relative to blood, drug distribution between the cells and the interstitial fluid of the brain (apart from active transport this might be influenced by pH and electrical potential differences between intracellular and interstitial fluids) and removal of the drug from the brain by the 'sink action' of the CSF. In addition, biological degradation of drugs is likely to be more important in long-term studies than in short-term studies.

Young et al (1988) obtained blood–brain distribution coefficients, defined by equation 1, for 30 drug compounds using an in-vivo radio-assay method.

$$BB = \frac{[\text{concn of solute in brain}]}{[\text{concn of solute in blood}]} \quad (1)$$

For twenty diverse compounds correlation of logBB with $\log P_{oct}$ was very poor, but there was better correlation with $\Delta\log P$, giving n = 20, $\rho = 0{\cdot}831$, s.d. = 0·44 and $F = 40$.

The problem with the above equations for log PS and logBB is that they lead to little quantitative understanding of the factors that influence brain penetration. A new approach (Abraham 1993) to the problem of blood–brain distribution has recently been described by Abraham et al (1994a) and the purpose of this study was to investigate whether this new methodology could be used to correlate kinetic transfer rates across the blood–brain barrier.

Materials and Methods

Model compounds

A chemically diverse set of model compounds covering a range of size and hydrophobicity were selected (Table 1). Compounds **13–18** (Fig. 1) radiolabelled with [^{14}C] were provided by Zeneca Pharmaceuticals. The specific activity of each compound was between 10–100 mCi mmol^{-1}. [^{14}C]urea (52 mCi mmol^{-1}), [^{14}C]thiourea (57 mCi mmol^{-1}), [^{14}C]-ethanol (21 mCi mmol^{-1}), [^{3}H]thymine (53 Ci mmol^{-1}), [^{14}C]glycerol (43 mCi mmol^{-1}), [^{3}H]oestradiol (40 mCi mmol^{-1}) and [^{3}H]diazepam (84·8 Ci mmol^{-1}) were obtained from NEN Ltd (Boston, MA). [^{14}C]ethylene glycol (7·8 mCi mmol^{-1}) and [^{14}C]antipyrine (41·5 mCi mmol^{-1}) were obtained from Sigma (Poole, Dorset).

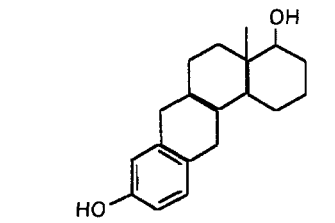
Measurement of blood–brain barrier permeability

Uptake into the brain of each test compound was measured using a short-duration vascular perfusion method (Takasato et al 1984; Deane & Bradbury 1990) as modified and described in detail by Gratton et al (1993). In brief, female Wistar rats were

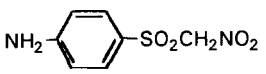
Table 1. $\log P_{oct}$, PS-product and solute descriptor* values for the test compounds.

	Compound	pK_a	$\log P_{oct}$†	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	V_X	Log PS Calc.	Log PS Obs.	PS (obs) × 10^{-3} (± s.e.m.)	n
1	Erythritol		−2·29	0·620	1·20	0·70	1·40	0·9070	−3·90	−4·57	0·027 ± 0·005	5
2	Urea		−2·11	0·500	1·00	0·50	0·90	0·4648	−3·69	−3·79	0·162 ± 0·042	6
3	Ethylene glycol		−1·36	0·404	0·90	0·58	0·78	0·5078	−3·10	−2·99	1·030 ± 0·075	6
4	Thiourea		−1·02	0·640	0·70	0·78	0·86	0·5696	−2·56	−3·36	0·433 ± 0·097	18
5	2-Propanol		0·05	0·212	0·36	0·33	0·56	0·5900	−1·34	−1·66	22·00 ± 4·00	5
6	Ethanol		−0·30	0·246	0·42	0·37	0·48	0·4491	−1·67	−1·523	0·00 ± 2·00	6
7	Antipyrine	1·4	0·20	1·320	1·50	0·00	1·48	1·5502	−2·02	−2·00	10·1·00	10
8	Mannitol		−3·20	0·836	1·80	0·70	1·92	1·3062	−5·00	−5·01	0·010 ± 0·003	6
9	Sucrose		−3·70	1·970	2·50	2·10	3·20	2·2279	−5·96	−5·30	0·005 ± 0·0004	6
10	Oestradiol		2·69	1·800	3·30	0·88	0·95	2·1988	−1·38	−0·83	148·00 ± 6·00	10
11	Thymine		−0·62	0·800	1·00	0·44	1·03	0·8925	−2·40	−1·93	11·740 ± 3·65	5
12	22001	5·30	1·55	1·710	1·30	0·40	1·10	1·4120	−0·74	−0·82	151·80 ± 12·66	6
13	12002	3·20	3·80	2·561	2·11	0·60	1·20	2·2620	0·92	0·71	5100 ± 500	7
14	11003	8·10	3·63	2·121	3·78	0·73	2·57	3·9830	−0·68	−0·75	176·6 ± 1·80	6
15	95005	7·95	1·26	1·354	2·46	0·77	1·50	2·0770	−2·11	−1·95	11·1 ± 0·73	6
16	26006	8·91	3·90	3·353	5·29	2·08	3·11	4·7800	−1·44	−1·79	16·30 ± 7·67	6
17	13007	10·10	2·19	0·673	0·55	0·16	0·61	1·1510	0·37	1·13	1·3500 ± 1050	5
18	Propranolol	9·40	3·65	1·843	1·50	0·60	1·27	2·1480	0·95	0·98	9600 ± 680	6

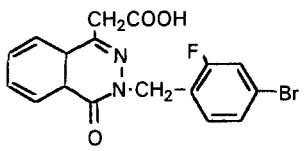
*P_{oct}, octanol–water partition coefficient; R_2, excess molar refraction; π_2^H, solute dipolarity or polarizability; α_2^H and β_2^H, hydrogen bond acidity or basicity; V_X, solute McGowan volume; PS, permeability of the blood–brain barrier. The descriptor values from Abraham (1993) or calculated as described in Abraham & Chadha (1996). †$\log P_{oct}$ values were from the Pomona (Claremont, CA, 91711) Medicinal Chemistry Project except for values for compounds **12** and **13** which were calculated from the given descriptors and a regression equation (Abraham & Chadha 1996) for $\log P_{oct}$.



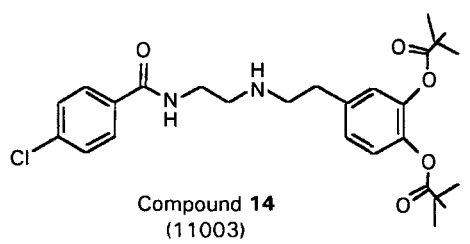
Compound **10**
(oestradiol)



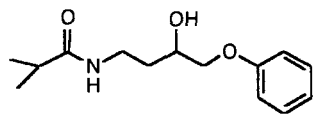
Compound **12**
(22001)



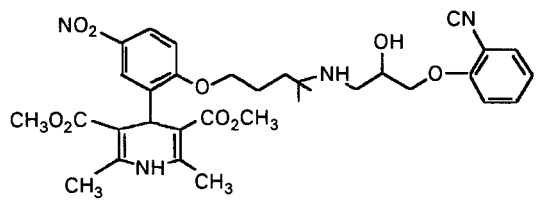
Compound **13**
(12002)



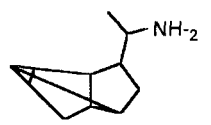
Compound **14**
(11003)



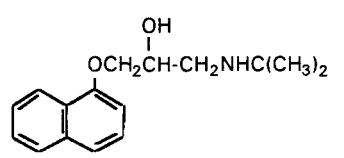
Compound **15**
(95005)



Compound **16**
(26006)



Compound **17**
(13007)



Compound **18**
(propranolol)

FIG 1. The structures of compounds **10** and **12** to **18**.

anaesthetized with pentobarbitone (4 mg/100 g, i.p.). The right common carotid artery was cannulated for perfusion of the internal carotid artery. Immediately the cannula was in place the heart was stopped by severing the ventricles and infusion was started. The animals were perfused at an infusion rate of 0·1 mL s^{-1} to give a net carotid perfusion pressure of 80 mmHg. Perfusion was performed using a protein-free bicarbonate-buffered saline to which the [^{14}C]- or [^{3}H]-labelled compound was added and equilibrated at 37·5°C. For highly permeable compounds, [^{3}H]diazepam (0·5 μCi mL^{-1}) was also added to the perfusate for measurement of the regional rate of fluid flow. At a net carotid perfusion pressure of 80 mmHg, mean perfusion fluid flow rate in the frontal cortex was 0·045 ± 0·002 (s.e.m., n = 18) mL s^{-1} g^{-1}. To verify that uptake for each tracer was unidirectional, uptake was measured at several perfusion times, ranging from 10 to 240 s, depending on the permeability of the test compound. For slowly penetrating solutes [^{3}H]inulin (2 μCi mL^{-1}) was added to the perfusate for determination of residual intravascular volume. The value of the mean intravascular volume (0·019 ± 0·002 (s.e.m., n = 15) mL g^{-1}) was used to correct the uptake spaces of the highly permeable flow-limited tracers.

Validation studies performed in our laboratory demonstrated that the regional rate of fluid flow and intravascular volume in the frontal cortex remains constant over the range of perfusion times used to measure uptake. Rates of uptake into the frontal cortex, expressed as a permeability surface area (PS) product (mL s^{-1} g^{-1}), were calculated by the single-time-point method of Ohno et al (1978), using perfusion times selected to minimize back-diffusion:

$$PS = -F_{pf} \ln(1 - (C_{tis(t)}/tF_{pf}C_{pf}) \quad (2)$$

where F_{pf} is the perfusion fluid flow-rate (mL s^{-1} g^{-1}), C_{tis} is the concentration of tracer in the frontal cortex minus intravascular radioactivity (d min^{-1} g^{-1}), C_{pf} is the concentration of tracer in the perfusate (d min^{-1} mL^{-1}) and t is the perfusion time (s). For slowly penetrating solutes, for which PS < 10% of perfusion fluid flow, equation 2 can be reduced to:

$$PS = C_{tis(t)}/tC_{pf} \quad (3)$$

It has been assumed that uptake of the compounds is by passive diffusion. Altering tracer concentration in the perfusate (up to 50-fold) had no effect on the calculated PS-product values for any of the test compounds (data not shown). It should be noted that for the more permeable compounds flow correction leads

to an increase in the PS-product obtained from equation 3. The greatest ratios for flow-corrected PS-product over the values given by equation 3 were for oestradiol and propranolol, 2·4 and 2·2 times, respectively. These high ratios are possible because of the high flows, about 4 times in-vivo values (Gratton et al 1993), obtainable during perfusion with physiological salt solution which is less viscous than blood.

The LFER methodology

The general linear free energy relationship (LFER) that we use can be expressed (Abraham 1993) as:

$$\log SP = c + rR_2 + s\pi_2^H + a\sum\alpha_2^H + b\sum\beta_2^H + vV_X \quad (4)$$

where SP is some property of a series of solutes in a given system and the explanatory variables or descriptors are solute properties: R_2 ($dm^3\ mol^{-1}/10$) is an excess molar refraction, π_2^H is the solute dipolarity/polarizability, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are the solute overall hydrogen-bonding acidity and basicity, respectively, and V_X ($dm^3\ mol^{-1}/100$) is the McGowan characteristic volume (Abraham & McGowan 1987); π_2^H, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are derived from equilibrium constants, as logK values, and have no units. The determination of descriptors from experimental water–solvent partition coefficients has been set out in detail (Abraham & Chadha 1996), and estimation of the descriptors from compound structure has also been described (Abraham et al 1994a, 1995; Abraham & Chadha 1996).

Abraham et al (1994a) applied equation 4 to 57 logBB values, leading to:

$$\log BB = -0{\cdot}04 + 0{\cdot}20R_2 - 0{\cdot}69\pi_2^H - 0{\cdot}71\sum\alpha_2^H \quad (5)$$
$$\qquad\quad 0{\cdot}06 \quad 0{\cdot}10 \qquad 0{\cdot}12 \qquad 0{\cdot}13$$
$$-0{\cdot}70\sum\beta_2^H + 1{\cdot}00V_X$$
$$\qquad\quad 0{\cdot}11 \qquad\quad 0{\cdot}10$$

$n = 57$, $\rho = 0{\cdot}9522$, s.d. $= 0{\cdot}20$, $F = 99$

In equation 5 the s.d. values for the coefficients are given under the coefficients themselves. This equation shows, for the first time, exactly which solute factors influence the distribution between blood and brain. Solute dipolarity, hydrogen-bond acidity, and hydrogen-bond basicity all reduce the logBB value and favour blood, whereas solute excess molar refraction (marginally) and solute size increase logBB and favour brain.

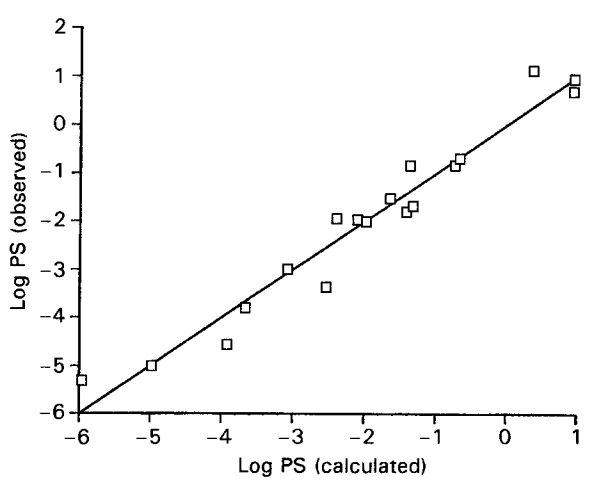


FIG. 2. Log plot of observed permeability surface area (PS)-product (mL s^{-1} g^{-1}) for all 18 compounds against PS-product calculated by use of equation 6.

Analysis of drug transfer across the blood–brain barrier

Correlation of solute descriptors with permeability-surface area (PS)-products. The PS-products for 18 varied solutes are listed in Table 1, and refer to values for the neutral species. Also given are the corresponding $\log P_{oct}$ values, again for the neutral species. Occasionally experimental $\log P_{oct}$ values were not available, and so we calculated $\log P_{oct}$ using the descriptors in Table 1 and our regression equation (Abraham & Chadha 1996) for $\log P_{oct}$. Descriptors for a few of the 18 compounds were available (Abraham et al 1994a; Abraham & Chadha 1996) and those for the remaining compounds were assigned either from known partition coefficients as shown elsewhere (Abraham & Chadha 1996) or by the addition of fragments (Abraham et al 1994a, 1995; Abraham & Chadha 1996). The descriptors used are given in Table 1. Application of equation 4 to the PS-product, as logPS, for 18 solutes leads to:

$$\log PS = -1{\cdot}21 + 0{\cdot}77R_2 - 1{\cdot}87\pi_2^H - 2{\cdot}80\sum\beta_2^H + 3{\cdot}31V_X \quad (6)$$
$$\qquad\quad 0{\cdot}24 \quad 0{\cdot}32 \qquad 0{\cdot}29 \qquad 0{\cdot}24 \qquad\quad 0{\cdot}37$$

$n = 18$, $\rho = 0{\cdot}9760$, s.d. $= 0{\cdot}481$, $F = 65$

In equation 6 the s.d. values for the coefficients are given under the coefficients themselves. The term in $\Sigma\alpha_2^H$ was significant at the 2% level only, and so has been omitted from equation 6. All the remaining terms are significant at the 96·6% level, or better. Equation 6 shows that solute excess molar refraction (weakly) and solute volume (strongly) lead to an increase in logPS, whereas solute dipolarity/polarizability and especially solute hydrogen-bond basicity lead to a decrease in logPS. A comparison with the logBB equation 5 is not straightforward, because equation 5 refers to a distribution in the blood–brain system whereas equation 6 refers to a rate process in the saline brain system. However, with the exception of $\Sigma\alpha_2^H$ the various solute descriptors influence the two different processes in qualitatively the same way. The main common factors are solute dipolarity/polarizability and solute hydrogen-bond basicity that favour blood or saline, and solute excess molar refraction and solute volume that favour brain.

The increase in logPS with solute size, equation 6, might seem paradoxical in comparison with simple passive diffusion. Certainly, the Stokes–Einstein equation relates the diffusion coefficient of a solute to the inverse of the solute radius, but this refers to diffusion in a solvent continuum. Diffusion of solutes across liquid phase boundaries is much more complicated, and van de Waterbeemd et al (1981) and Dearden (1990) note situations in which water-to-solvent diffusion coefficients increase with increasing solute size, and can also be completely independent of solute. We have found that water-to-human skin permeability coefficients also increase with increasing solute size (Abraham et al 1995). Because water is known to be more acidic than brain (Abraham & Weathersby 1994) it is not surprising that solute basicity retards transport from saline to brain. The lack of the $\Sigma\alpha_2^H$ descriptor in equation 6 is puzzling, because water is also known to be more basic than brain, and we might have expected that solute hydrogen-bond acidity would retard transport. The lack of the $\Sigma\alpha_2^H$ term in equation 6 is not simply because of lack of strong hydrogen-bond acidic solutes, because many solutes in Table 1

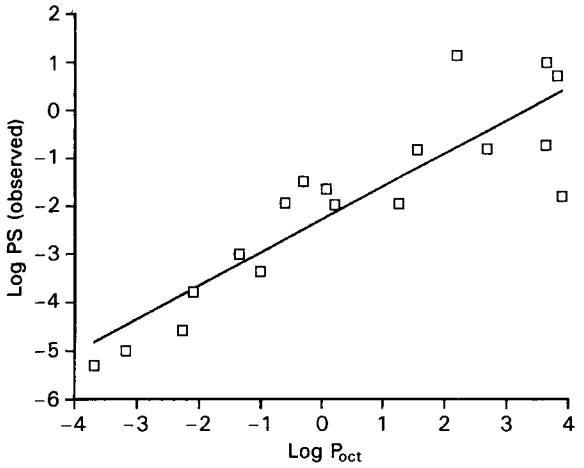


FIG. 3. Log plot of permeability surface area (PS)-product (mL s^{-1} g^{-1}) for all 18 compounds against octanol–water partition coefficient (P_{oct}).

are strong hydrogen-bond acids (note that symbol $\Sigma\alpha_2^H$ for acetic acid is 0·61 and for phenol is 0·6), and solutes 9 and 16 are very strong indeed. It has long been realized that the rate of entry of a compound into a cell depends on its ability to partition into the lipid cell membrane (Davson & Danielli 1943). In the blood–brain system compounds must, of course, cross the luminal and abluminal membranes of the capillary endothelium. Hence, the same capacity to dissolve in the lipid membranes must be crucial in determining the rate of entry into the brain across the blood–brain barrier. The positive influence of the descriptors R_2 and V_X, and the negative influence of the descriptors π_2^H and $\Sigma\alpha_2^H$ are between 2·7 and 4 times greater in the equation for rate (equation 6) than in that for steady-state distribution (equation 5). This must be because of the key role of lipid membrane solubility in determining the rate of blood–brain penetration. For steady-state distribution, lipid solubility is again important, e.g. because of partitioning of drugs into CNS cell membranes, but there will also be a major influence in the opposite direction from solute distributed in the water phase of the brain. A plot of observed logPS against logPS calculated from equation 6 is shown in Fig. 2. No compounds have been omitted, and there is random scatter about the line of identity. Furthermore, there is no suggestion of a 'plateau' or of a parabolic-type relationship in the high-logPS region; the line of identity is maintained throughout (see Fig. 2).

Relationship between octanol–water partition coefficient and logPS and logBB. LogPS is plotted against $\log P_{oct}$ in Fig. 3. A simple regression of logPS against $\log P_{oct}$ yields the equation:

$$\log PS = -2{\cdot}28 + 0{\cdot}69\ \log P_{oct} \quad (7)$$

n = 18, ρ = 0·8815, s.d. = 0·94, F = 55

Equation 7 is much better than the equation for blood–brain distribution, equation 5, but even so logPS is correlated to only 0·94 log units, and the scatter about the line of identity is no longer random. A parabolic relationship leads to the equation:

$$\log PS = -1{\cdot}81 + 0{\cdot}75\ \log P_{oct} - 0{\cdot}084(\log P_{oct})^2 \quad (8)$$

n = 18, ρ = 0·9106, s.d. = 0·85, F = 36

The s.d. value of 0·85 log units in equation 8 is too large for the equation to be of any real predictive value and the parabolic fit leads to a calculated maximum of log PS at $\log P_{oct} = 4{\cdot}5$ units. Whether or not there actually is a parabolic relationship between log PS and $\log P_{oct}$ is doubtful; the F-statistic is lower for equation 8 than for equation 7, and the squared term in equation 8 is significant at only the 95% level. For blood–brain distribution, the experimental values of logBB (Abraham et al 1994a) fit equation 5 with no sign of any unusual distribution about the line of identity, the regression equation against $\log P_{oct}$ is very poor, and we find no parabolic relationship with $\log P_{oct}$:

$$\log BB = -0{\cdot}34 + 0{\cdot}17\ \log P_{oct} + 0{\cdot}013(\log P_{oct})^2 \quad (9)$$

n = 50, ρ = 0·5454, s.d. = 0·51, F = 10

The correlations of logBB and logPS with $\log P_{oct}$ are therefore quite different; for logBB there is only a very poor correlation (Young et al 1988; Abraham et al 1994a) but for logPS there is a more reasonable correlation, as is shown in equation 7. We can account for this difference through our correlation equation (Abraham et al 1994b) for $\log P_{oct}$:

$$\log P_{oct} = 0{\cdot}088 + 0{\cdot}562R_2 - 1{\cdot}054\pi_2^H + 0{\cdot}034\Sigma\alpha_2^H - 3{\cdot}460\Sigma\alpha_2^H + 3{\cdot}814V_X \quad (10)$$

n = 613, ρ = 0·9974, s.d. 0·116, F = 23162

It can be seen that the $\Sigma\alpha_2^H$ term in equation 10 is insignificant, exactly as in the logPS equation, equation 6, but in contrast with the logBB equation, equation 5. It is the presence of a significant $\Sigma\alpha_2^H$ term in equation 5 that is a major reason for the lack of correlation of logBB with log P_{oct}.

Conclusions

The pharmaceutical literature is confusing because measures based on biological activity (Hansch et al 1968) or on drug-receptor interaction (Laduron et al 1982; Awouters et al 1983) have been used as an indication of the ability of a drug to cross the blood–brain barrier. Such measures must inevitably be composite in nature, being related to efficacy of binding or interaction with some receptors on brain cells, and to either a rate or an equilibrium transport across the blood–brain barrier. To obtain any meaningful correlation of brain penetration or the ability to cross the blood–brain barrier with physicochemical descriptors it is essential to deal with one particular measure at a time. Either short-term rate studies or long-term equilibrium studies seem suitable measures for use in correlation analysis. If mixtures of measures are used, it becomes difficult to reach any conclusion. For example, a recent attempt was made (Seelig et al 1994) to relate the ability of drugs to cross the blood–brain barrier with the lipophilicity of the drug. However, the measures that were used, as judged by quoted references, varied from studies on tissue and plasma distribution (Heykants et al 1974) to binding studies (Awouters et al 1983). Not surprisingly, no general relationship was found. The oft-quoted (Gupta 1989) rule that an octanol-water partition coefficient, $\log P_{oct}$, of approximately 2 log units is optimum for ready entry into the brain (Hansch et al 1987) is derived, not from rates of permeation nor from equilibria, but from studies on biological activity, for example the potency of hypnotics acting as CNS depressants. It could be that, if the concentration of drug in the interstitial fluid to which receptors on the brain cells are exposed is related to blood or plasma concentration, the ratio might bear a parabolic relationship to P_{oct}. Indeed such a hypothesis might be accessible to study with recent techniques

such a microdialysis. At present no series of suitable results are available for analysis. Our conclusion is that there is no parabolic relationship between log BB and $\log P_{oct}$, and that the rule of a maximum $\log P_{oct} = 2$ does not apply to blood–brain distribution. There might (just) be such a relationship between log PS and $\log P_{oct}$, but further work will be needed to confirm or reject this for our saline–brain PS values. In any case, the parabolic relationship, if it exists, between logPS and $\log P_{oct}$ is not good enough to use predictively. On the other hand, the general equation 6 can be applied to logBB and logPS values, as a predictive and interpretative equation.

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