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Research Article

Drug Equilibration Across the Blood-Brain Barrier—Pharmacokinetic Considerations Based on the Microdialysis Method[1]

Margareta Hammarlund-Udenaes,[2,4] Lennart K. Paalzow,[2] and Elizabeth C. M. de Lange[3]

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Purpose. The purpose of the study was to investigate the influence of different rates of transport into and out of the brain, including passive and active transport, on unbound brain concentrations and profile in relation to the blood concentration profile. Special emphasis is put on hydrophilic drugs.

Methods. Simulations were performed with a model including one body compartment and one brain compartment, with linear or saturable transport into and out of the brain. Comparisons were made with experimental results from microdialysis (MD) studies.

Results. Three features were evident when combining the MD results: 1) equilibration across the blood-brain barrier (BBB) is rapid, 2) half-life is similar in brain and blood for most drugs, and 3) unbound brain concentrations seldom reach the level of unbound blood concentrations. A low concentration ratio brain:blood is not mainly caused by a low influx, but rather by different influx and efflux clearances. Active transport out of the brain can explain the results, but also active transport into the brain under certain conditions. A small volume of distribution in brain vs. that in the rest of the body contributes to a rapid equilibration and similar half-lives.

Conclusions. Assumptions of slow equilibration of hydrophilic drugs and similar unbound concentrations across the BBB at steady state are contradicted. The results are more in line with recent findings on the presence of P-glycoprotein and other transport mechanisms at the BBB. Non-passive transport across the BBB seems to be the case for almost all drugs studies with MD so far.

KEY WORDS: microdialysis; blood-brain barrier transport; pharmacokinetics; drug equilibration.

INTRODUCTION

Drug transport into the brain is limited by the blood-brain barrier (BBB) and is dependent on physico-chemical factors of the drug such as lipophilicity, ionisation and pH in relation to membrane properties. The concentration time profile and the concentration level in brain in turn determines the pharmacodynamic effect over time.

For most drugs the rate of penetration into brain tissues is limited by diffusion of the drug across the BBB (1). The rate of equilibration is determined by the perfusion rate and by the distribution ratio. In general, time to equilibrium depends on partition coefficient, blood flow to a particular tissue and the volume of that tissue. The work by Brodie *et al.* (1) studying the influence of lipid solubility on the passage of drugs into the cerebrospinal fluid (CSF) is the basis for the understanding of equilibration also across the BBB. The results imply that it takes longer for hydrophilic drugs to reach equilibrium at conditions of constant blood concentration than for more lipophilic drugs. A slower time-profile in the brain compared to blood with a later time for maximal concentration (t_{max}) and perhaps a longer half-life in brain compared to blood is to be expected.

During the last years, microdialysis has emerged as a method by which it is experimentally possible to measure unbound concentrations on each side of the BBB in one animal over time. Brain extracellular fluid (ECF) and blood profiles determined with microdialysis in most cases present half-lives that are similar in brain and blood and times for maximal concentrations (t_{max}) in brain that are quite close to t_{max} in

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[2] Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, Faculty of Pharmacy, University of Uppsala, Uppsala, Sweden.

[3] Division of Pharmacology, Leiden/Amsterdam Centre for Drug Research, Leiden University, Leiden, The Netherlands.

[4] To whom correspondence should be addressed. (e-mail: Margareta.Hammarlund-Udenaes@biof.uu.se)

ABBREVIATIONS: BBB, blood-brain barrier; AUC, area under the concentration time curve; k, rate constants; CL, clearance; Tm, maximum transport rate; Km, concentration at half-maximal transport rate; MD, microdialysis; V, volume of distribution; t_{max}, time for maximum concentration; C_{max}, maximum concentration. *Subscripts*: blood, describing the blood (body) compartment outside the brain; brain, describing the brain compartment; el, elimination from the body; in, into the brain; out, out of the brain.

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blood. Among the examples are atenolol and acetaminophen (2), zidovudine (3,4) and theophylline (5). Carbamazepin differs from the others with a longer half-life in brain than in blood and a later t_{max} (6), as does SDZ EAA 494 (7). Zidovudine was reported by Ståhle *et al.* to have a longer half-life in brain than in blood of rats, which contradicts the results above (8).

For many drugs (both hydrophilic and lipophilic) microdialysis results reveal that the unbound brain concentrations are much lower than the corresponding blood concentrations, eg. atenolol and acetaminophen (2), baclofen (9), caffeine and theophylline (10), EAB515 (11), gabapentin (12), methotrexate (13), rhodamine-123 (14), theophylline (5) and zidovudine (3,4,8). For some lipophilic drugs the concentrations are reported to be similar, eg. diazepam (15), diazepam, nordiazepam, and oxazepam (16), tacrine (17). Carbamazepin has an area ratio of one (6).

Caution should however be used when interpreting some of the microdialysis results. Most studies have used *in vivo* recovery methods in both blood and brain, which is optimal for describing surrounding drug concentrations. Others have performed *in vitro* recovery prior to probe insertion (and in some cases also after removal of the probe), which gives a different recovery than the one *in vivo* (2,9,13,15–17), although Deguchi *et al.* use a modified *in vitro* recovery method (9).

The present paper focuses on pharmacokinetic profiles in brain vs. those in blood from a theoretical point of view and relates this to what has been observed with microdialysis experiments. Simulations are used to describe unbound brain concentration time profiles in relation to unbound blood profiles. The effects of passive, as well as active transports into and out of the brain are investigated.

RELATIONSHIPS

Clearances

Unbound drug concentrations in blood, $C_{u,blood}$, and brain, $C_{u,brain}$, are described by the following differential equations (one body compartment and one brain compartment) (Fig. 1a):

$$V * dC_{u,blood}/dt = R_{inf} - CL * C_{u,blood} - CL_{in} * C_{u,blood} + CL_{out} * C_{u,brain} \quad (1)$$

and

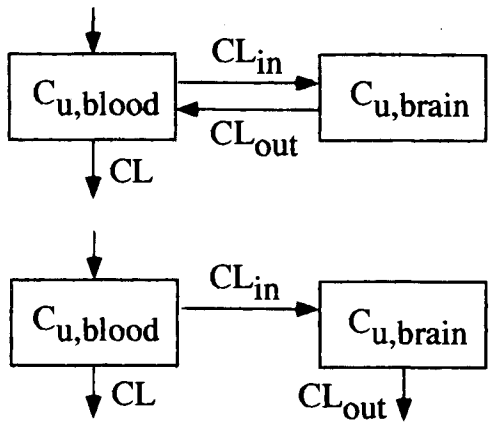

Fig. 1. Model for blood and brain compartments. a) Regular model, b) Model as used in the simulations.

$$V_{brain} * dC_{u,brain}/dt = CL_{in} * C_{u,blood} - CL_{out} * C_{u,brain} \quad (2)$$

where V and V_{brain} are the apparent volumes of distribution of unbound drug in the body and in the brain, CL is the clearance from the body and CL_{in} and CL_{out} are diffusional clearances into and out of the brain. CL_{out} represent transport from brain back to blood via the BBB membrane but could also include other mechanisms of transport or elimination, eg. metabolism within the brain, which is relevant for some compounds, or bulk flow to the CSF.

At equilibrium, the rate of change of concentrations in the brain is zero and therefore $CL_{in} * C_{u,blood} = CL_{out} * C_{u,brain}$. For a single dose this can be expressed as:

$$CL_{in}/CL_{out} = AUC_{u,brain}/AUC_{u,blood} \quad (3)$$

where AUC is the area under the concentration time curve.

If the drug is solely transported by passive diffusion across the BBB, $C_{u,brain}$ and $C_{u,blood}$ will be equal at equilibrium and comparably $AUC_{u,brain}$ and $AUC_{u,blood}$ will be the same ($CL_{in} = CL_{out}$). If the drug is more rapidly eliminated from the brain than transported into the brain, $AUC_{u,brain}$ will be smaller than $AUC_{u,blood}$ due to CL_{out} being larger than CL_{in}. To some extent the latter is always true, due to the presence of the bulk flow.

Rate Constants

When observing drug concentration profiles in the brain and blood the processes can also be described by rate constants:

$$V * dC_{u,blood}/dt = R_{inf} - k_{el} * V * C_{u,blood} - k_{in} * V * C_{u,blood} + k_{out} * V_{brain} * C_{u,brain} \quad (4)$$

and

$$V_{brain} * dC_{u,brain}/dt = k_{in} * V * C_{u,blood} - k_{out} * V_{brain} * C_{u,brain} \quad (5)$$

where the rate constants k_{el}, equal to CL/V, describes elimination from the body, k_{in}, equal to CL_{in}/V, describes transport into the brain, and k_{out}, equal to CL_{out}/V_{brain}, describes elimination from the brain. Please note that the comparison of k_{in} and k_{out} in relation to CL_{in} and CL_{out} is complicated by the volume of the reference site (blood or brain).

Physiologically, the brain in humans constitutes about 2% of the body volume (18). Regarding apparent volumes of distribution in the body, tissue binding in relation to protein binding in blood determines the size. In the present paper unbound concentrations and apparent unbound volumes of distribution are discussed. If no binding or cellular distribution in brain occurs, V_{brain} equals the physiological volume of ECF in brain. If there is binding within the brain, V_{brain} is larger.

For practical purposes we assume that V_{brain} is 1% of V, meaning that the amount of drug present in the brain at equilibrium ($V_{brain} * C_{u,brain}$) is 100 times smaller than in the rest of the body ($V * C_{u,blood}$). The brain tissue will thus take minute amounts of drug from blood and will consequently not affect the concentration time profile in blood. The transport of drug into and out of the brain can therefore be modelled where blood concentration is the driving force for brain concentrations, without the uptake into or elimination from the brain influencing

the blood profile (Fig 1b). This approach is similar to what is done in calculations of brain distribution (12,19,20). The differential equation describing the blood compartment can be simplified to:

$$V * dC_{u,blood}/dt = R_{inf} - CL * C_{u,blood} \quad (6)$$

The brain compartment is still described by Equation 2. For passive transport, $CL_{in} = CL_{out}$ is assumed.

If there is an active (saturable) uptake into the brain and a passive transport out of the brain, the differential equation for the brain compartment can be written as

$$V_{brain} * dC_{u,brain}/dt = (T_{m,in}/(K_{m,in} + C_{u,blood})) * C_{u,blood} - CL_{out} * C_{u,brain} \quad (7)$$

where T_m is the maximal transport rate and K_m is the blood concentration for half-maximal transport.

If, on the other hand, there is an active (saturable) transport out of the brain and a passive transport into the brain, the equation can be written as:

$$V_{brain} * dC_{u,brain}/dt = CL_{in} * C_{u,blood} - (T_{m,out}/(K_{m,out} + C_{u,brain})) * C_{u,brain} \quad (8)$$

where $K_{m,out}$ is the brain concentration for half-maximal transport. A more realistic alternative to Equation 8 is a passive component both into and out of the brain ($CL_{in} = CL_{out}$) and an additional active transport out. This can be written as:

$$V_{brain} * dC_{u,brain}/dt = CL_{in} * C_{u,blood} - CL_{out} * C_{u,brain} - (T_{m,out}/(K_{m,out} + C_{u,brain})) * C_{u,brain} \quad (9)$$

CL_{in} as discussed in the present paper is based on unbound concentrations in blood and brain. In comparison with the traditional way of presenting BBB transport of drugs by the permeability surface area product (PS) this should be taken into account (21,22). PS is normally expressed per g of brain tissue (ml * min^{-1} * g^{-1}) and relates to total brain concentrations.

SIMULATIONS AND INTERPRETATIONS OF THE RESULTS

To investigate the influence of different rates of transport into and out of the brain on brain unbound drug levels and profiles, simulations were performed with different relationships between CL_{in}, CL_{out} and CL. Also, active (saturable) transport into and out of the brain was simulated. For purpose of clarity, one compartment was used for the body and one for the brain (Fig. 1b). Simulations were performed with the program IThink® (Stella®) on a MacIntosh computer. If not otherwise stated, R_{inf} was 10 000 with an infusion time of 10 minutes. V was set to 100, V_{brain} was set to 1 and CL was set to 10 (i.e. k_{el} was 0.1). The simulations were performed with the Euler's integration method and a Δt of 0.1. The total time was 90 minutes.

Linear Transport into and out of the Brain

$CL_{in} = CL_{out}$

Fig. 2 shows a situation where $CL_{in} = CL_{out}$ (Eq. 2 and 6), i.e. passive transport. Decreasing CL_{in} and CL_{out} from 1.0 to 0.01 changed the profile in brain vs. blood towards later t_{max} and longer half-life in brain, as expected with increasing hydrophilicity. When $k_{out} > k_{el}$, half-life in brain is determined by half-life in blood. When $k_{out} < k_{el}$, half-life in brain is independent of half-life in blood. In all cases, $AUC_{brain} = AUC_{blood}$.

The half-life in the body is determined by k_{el} (CL/V). The half-life in the brain is determined by the slowest step of k_{el} or k_{out} (CL_{out}/V_{brain}). Due to the much smaller volume of distribution in the brain compared to that of the rest of the body, CL_{out} can be substantially smaller than CL (1/100 in our example) and still the elimination from the body will determine the half-life in brain. If passive diffusion is the process for transport across the BBB both ways, the AUC in brain vs that in blood should always be equal. When drug half-life in the body is very short, the limit where $k_{out}^2 \leq k_{el}$ comes closer. For these drugs there would be a higher probability of finding longer half-lives in brain than in blood.

$CL_{in} < CL_{out}$

To describe the influence of CL_{in} vs. CL_{out} on the profile in brain vs. that in blood, CL_{out} was set to 0.5 (Fig. 3). Decreasing values of CL_{in} from 0.5 to 0.001 lowered the level of drug in the brain but did not change the time-aspects of drug concentration (same t_{max}, same half-life, in this case the same half-life as in blood, as $k_{el} < k_{out}$). With smaller CL_{in}, the AUC ratio becomes lower.

In summary, the half-life in brain is determined by CL_{out}/V_{brain}, in relation to CL/V, while the concentration reached in brain is determined by CL_{in}. A $CL_{in} < CL_{out}$ is likely due to the presence of bulk flow (ECF drainage). Metabolism within the brain might also give a higher CL_{out}. Active transport into or out of the brain are simulated below.

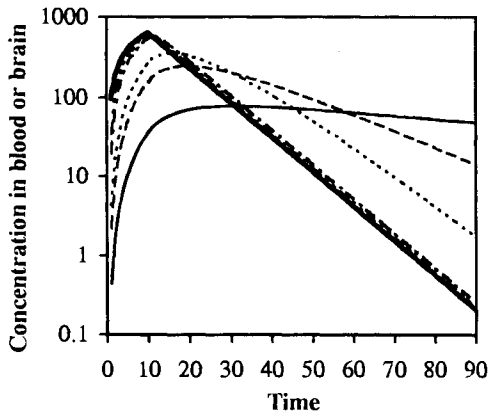

Fig. 2. Simulations of brain concentrations for linear transport into and out of the brain after systemic administration. Blood (thick line), brain (thin lines) with CL_{in} and CL_{out} being similar with values of 1.0 (-·-·-), 0.5 (-·-·-), 0.1 (·····) 0.05 (---) and 0.01 (—). CL from the body is 10, V is 100 and V_{brain} is 1.

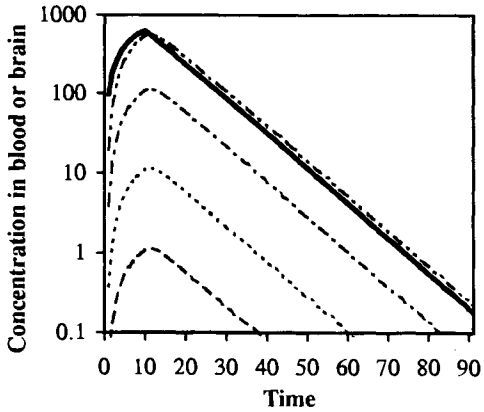

Fig. 3. Simulations of brain concentrations for different CL_{in} with a constant CL_{out} of 0.5. Blood (thick line), brain (thin lines) with CL_{in} being 0.5 (-···-), 0.1 (-·-·-), 0.01 (·····) and 0.001 (---). CL from the body is 10, V is 100 and V_{brain} is 1.

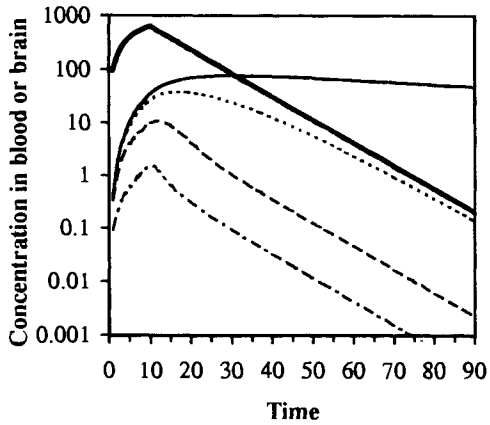

Fig. 5. Simulations of brain concentrations for linear transport into the brain and saturable plus linear transport out of the brain. CL_{in} and CL_{out} is 0.01 (solid thin line, cf. Fig. 2). Blood (thick line), brain (thin lines). $T_{m,out}/K_{m,out}$ is from the top 10/100 (·····), 10/10 (---) and 10/1 (-·-·-). CL from the body is 10, V is 100 and V_{brain} is 1.

Active Transport into the Brain

CL_{out} was set to 0.5. Two situations can be distinguished (Fig. 4, Eq. 7). When blood concentrations are below $K_{m,in}$, and $k_{out} > k_{el}$, brain concentrations behave linearily compared to blood concentrations. When blood concentrations are above $K_{m,in}$, the concentration in brain rapidly reach a constant level. This can be compared with a constant infusion of drug into the brain with a rate of $T_{m,in}$. Maximal concentrations in brain are in fact reached more rapidly than in blood. Depending on $T_{m,in}$, the concentration level differs (Fig. 4). This situation is to be compared with control of glucose level in brain vs. fluctuating levels in blood (23) and with other endogenous transport situations across the BBB. Although in the present simulations, CL_{out} is defined as being a passive process, it might as well include metabolism within the brain, as is the case for glucose (23). From Fig. 4 it is clear that $T_{m,in}$ has an elaborate control on the brain concentrations obtained. When $K_{m,in}$ is decreasing in relation to blood concentrations, the concentration in brain remains at a constant level for a longer period of time. Administering a dose that results in drug concentrations below $K_{m,in}$ would not make it possible to distinguish between active transport into and out of the brain, as will be discussed below.

Active Transport out of the Brain

Active transport out of the brain is simulated together with a passive component of the size of CL_{in} according to Eq. 9 (Fig. 5). CL_{in} was set to 0.01. Independent of the brain concentration in relation to $K_{m,out}$, the active component will reduce brain concentrations compared to what would be the case for a situation with only passive diffusion. Active transport out of the brain will, according to Fig. 5, change a slower profile in the brain to a more rapid one. Given a certain $T_{m,out}$, there is a smaller AUC ratio with smaller $K_{m,out}$. When $T_{m,out}$ is decreasing, thereby decreasing the influence of the active component in relation to the passive component, strange brain profiles are theoretically possible depending on the values of $T_{m,out}$ and $K_{m,out}$ in relation to brain concentration and CL_{out} (Fig. 6).

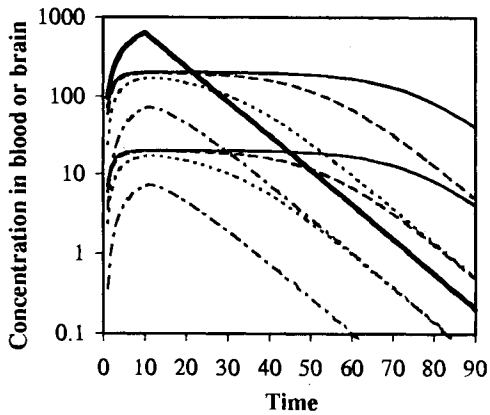

Fig. 4. Simulations of brain concentrations for saturable transport into the brain and passive transport out of the brain with a CL_{out} of 0.5. Blood (thick line), brain (thin lines) with from the top $T_{m,in}/K_{m,in}$ being 100/1 (—), 100/10 (---), 100/100 (·····), 100/1000 (-·-·-), 10/1 (—), 10/10 (---), 10/100 (·····) and 10/1000 (-·-·-). CL from the body is 10, V is 100 and V_{brain} is 1.

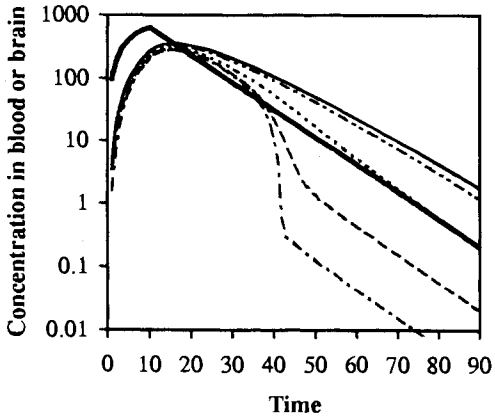

Fig. 6. Simulations of brain concentrations for linear transport into the brain and saturable plus linear transport out of the brain. CL_{in} and CL_{out} is 0.1 (thin line, cf. Fig. 2). $T_{m,out}/K_{m,out}$ is from the top 10/1000 (-·-·-), 10/1000 (·····), 10/10 (---) and 10/1 (-·-·-). CL from the body is 10, V is 100 and V_{brain} is 1. The difference in profile compared to Fig. 5 depends on $T_{m,out}$ rather than on the different size of CL_{in} and CL_{out}.

Pharmacokinetic principles can according to the present results be adapted to investigate the transport mechanisms of a drug across the BBB. If a drug is actively transported into the brain one can expect a rapid equilibration and constant levels in the brain in spite of changing blood concentrations if the blood concentrations are higher than $K_{m,in}$. The area ratio depends on the value of $T_{m,in}$ and blood concentrations in relation to $K_{m,in}$. If a drug is actively transported out of the brain the AUC ratio is always below unity compared to blood. The half-life in brain is still dependent on the relationship to the half-life out of the body and could theoretically be slower than in blood. It could however never be shorter, as the blood concentrations are the driving force for brain concentrations.

VERIFICATION OF THEORY

For all drugs studied so far with microdialysis, the AUC ratio between brain and blood is ≤ 1. Most drugs have a much smaller AUC in brain than in blood. The half-life in brain vs that in blood is similar with some exceptions (6–8). In this section, selected examples from the literature are discussed.

The unbound concentration of atenolol, which is very hydrophilic, was studied in cortical brain and blood by de Lange and coworkers, using the microdialysis technique (2). Atenolol rapidly reached maximal concentration within the brain and the concentration fell with the same half-life as that in blood (Fig. 7). The concentration in brain never reached that of blood. The AUC ratio was 4% (in vitro recovery in brain, regular blood samples). Based on Eq. 3, a much higher capacity for elimination from the brain than for entrance into the brain would explain the data on atenolol (active transport out—Fig. 5). This is in line with the findings of Agon et al who studied the transfer of atenolol across the BBB by PET (24). The passage of [^{11}C]atenolol could be described by a two-compartment model for plasma and brain ECF. Estimations indicated that the transfer rate constant from brain ECF to plasma (k_{out}) was

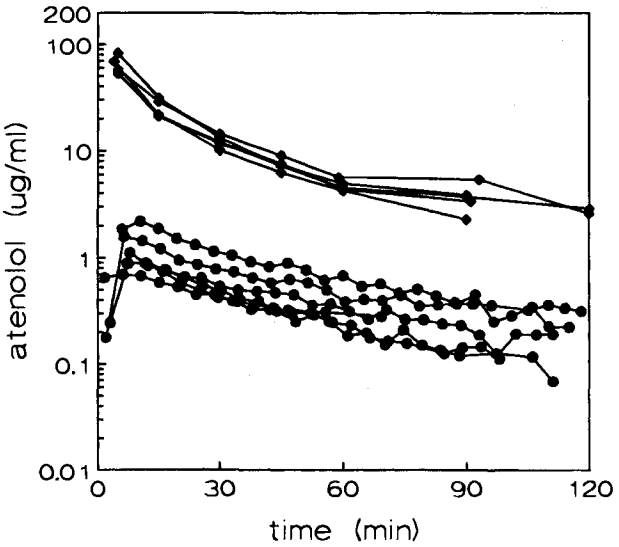

Fig. 7. Individual atenolol concentrations in brain and blood in the rat after i.v. administration, measured with microdialysis (regular blood samples (♦), transversal MD probe in cortex (●). From De Lange et al. (2) with kind permission of Elsevier Science-NL, Amsterdam, The Netherlands.

larger (6-fold) than that from plasma to brain ECF. Acetaminophen is more lipophilic than atenolol. The AUC ratio was higher, about 18%, but the interpretations are the same as for atenolol (2).

Caffeine was studied by Nakazono and coworkers (19). They were the first ones to model brain and CSF compartments based on microdialysis data. The recovery was based on total brain tissue concentrations and regular blood samples were drawn, which makes the data more difficult to compare with the rest. The rate constant out of the body, k_{el}, was smaller than k_{out} (0.013 vs 0.41) implying rate-limitation in the elimination from the body.

Carbamazepin displayed similar AUC in brain as in blood (6). The half-life of carbamazepin was 3.8 h in brain vs 2.2 in blood. Study time was 6 h. Passive transport into and out of the brain is assumed based on the AUC ratio. However, only one dose was studied and the profile of carbamazepin in brain could also from a theoretical point of view indicate active uptake, as the concentration in brain is persisting for a long time in spite of decreasing blood concentrations and at later times becomes more close to blood half-life (cf. Fig. 4). For the metabolite carbamazepin-10,11-epoxide, the ratio was 0.46 and the concentration in brain closely followed that in blood. The half-life was not significantly different in brain and blood.

Zidovudine has been extensively studied with microdialysis, showing the great potential of the method in understanding brain equilibration of drugs. Several doses of zidovudine was administered to rabbits (3). The AUC ratio between thalamus and blood was 5–9% and not significantly different between doses. When probenecid was added, the brain profile changed from parallel half-lifes to a situation where the concentrations slowly approached blood concentration (25). The steady state relationship between brain and plasma concentrations of zidovudine was 20% in dogs (26).

In a recent paper, an elegant approach to calculating the values of zidovudine brain transport parameters in rabbits was published by Wang and Sawchuk (20). It was found that CL_{in} was 0.03 ml/min*kg, while CL_{out} was 0.15 ml/min*kg. CL was 22 ml/min*kg. V (central volume in a two compartment model) was estimated in an earlier studies to be 510 ml/kg and V_{brain} was assumed to be similar to the physiological brain ECF volume of 2.9 ml/kg due to limited tissue distribution. The half-life in blood was 45 minutes. Calculation of the theoretically possible half-life in brain based on CL_{out} and V_{brain} gives a value of 13 minutes and from CSF 10 minutes. This is a clear example of the half-life in blood being the slowest step, influencing the rate of change of drug concentrations also in brain. The value of CL_{out} is much larger than the bulk flow of 0.0012 ml/min*kg. Also for gabapentin in rats, CL_{in} was smaller than CL_{out} (0.044 vs. 0.38 ml/min*g brain) (12). It is to be noted that V_{brain} for gabapentin was 5.5 ml/g brain (20 mL/kg) due to extensive brain distribution.

Probenecid has been used to influence the active transport of drugs across the BBB in microdialysis studies (9,25,27–29). Wong *et al.* (25) showed that zidovudine is secreted actively from the brain by a carrier mediated system and that probenecid inhibits this pathway to 73%. Deguchi and coworkers (9) observed an influence on baclofen transport by probenecid.

Another mechanism that eliminates certain drugs from the brain is P-glycoprotein (Pgp), being expressed on the luminal surface of the brain capillary endothelial cells (30–33).

Cyclosporine A coadministration with rhodamine-123 significantly increased the brain distribution of rhodamine-123 from 0.6% to 2.2% (3.6-fold), probably by inhibition of the P-glycoprotein efflux transporter (14). In the case of etoposide, its distribution across the BBB was not influenced by cyclosporine A (34). The authors concluded that the increased etoposide levels in the brain after coadministration of cyclosporine A was rather due to a decrease in the systemic clearance of etoposide and thereby a parallel increase in brain concentrations.

DISCUSSION

The aim of the present study was to investigate the rate and extent of equilibration between unbound brain and blood concentrations during different conditions of BBB influx and efflux (passive and active), after systemic administration of drugs. The simulations, combined with microdialysis data from the literature, show that active transport components across the BBB are most likely present for more drugs than expected.

For most drugs studied, microdialysis experiments have shown that the equilibration of drug concentrations between brain and blood is very rapid. The blood concentration profile is thereby a strong predictor for the concentration time profile in brain also for hydrophilic compounds. This contradicts earlier assumptions on hydrophilic drugs having a slow (passive) equilibration across the BBB due to low permeability. Thus, rate and mode of administration has as much higher influence on brain drug concentration profile and effects than expected. This information is important for conclusions on possible pharmacodynamic profiles of drugs acting in the brain. The results imply that an observed delay in central drug effect is more likely to be caused by pharmacodynamic processes than by a pharmacokinetic delay in distribution, as exemplified by gabapentin (35).

The ability of a drug to pass the BBB and thereby give rise to a certain drug concentration in the brain is dependent on CL_{in}. However, the half-life of the drug in the brain is solely determined by k_{out} in relation to the elimination from the body (Fig. 2 and 3). For most drugs studied so far with microdialysis, the half-life in brain is similar to the half-life in blood, implying $k_{out} > k_{el}$ to be the most common situation. This can be related to a small volume of distribution of the brain, V_{brain}, influencing the value of k_{out} vs. the size of V, influencing k_{el}.

The simulations verify that an AUC ratio < 1 can be explained by more efficient mechanisms for efflux from compared to influx into the brain ($CL_{in} < CL_{out}$). Possible mechanisms are active transport or bulk flow. Active transport out is the most probable explanation (9,12,14,20). Metabolism within the brain should also be considered (36). The quantitative importance of brain metabolism is not clarified. A low AUC ratio might also be caused by active transport into the brain with special relationships between blood concentrations, $T_{m,in}$ and $K_{m,in}$. This is less probable for the majority of drugs. Regarding the contribution of bulk flow for the larger CL_{out} than CL_{in}, it was clearly calculated, both for zidovudine (20) and gabapentin (12), that this contribution was minor compared to other processes. Whether bulk flow can explain the discrepancies for other drugs remains to be determined.

Which processes that are present for a certain drug can be investigated by administering different doses, different infusion rates and infusion times and compare the resulting AUC ratios and brain profiles. A slow increase in blood concentrations and more than one dose is of value when the purpose is to verify active transport into the brain. To investigate active transport out of the brain the concurrent administration of an inhibitor is important.

The simulations of the brain to plasma concentration profiles were made with the same type of model as the link-model suggested by Sheiner and coworkers (37), where the brain (effect) compartment is so small that it receives negligible amounts of drug and therefore does not influence the pharmacokinetics of the drug in the body as a whole (Fig. 1 b). According to the link model, the blood concentration profile together with k_{e0} reflects the kinetics of the drug at the site of action. When deriving the equations for the link-model it is often stated that CL_{in} is equal to CL_{out} (38), consequently at steady state it is assumed that C_{blood} equals $C_{effectsite}$. The true drug concentration at the site of action remains unknown. With microdialysis this can be measured. What is obvious from several publications is that $C_{u,brain}$ is often much lower than $C_{u,blood}$, thereby indicating that $CL_{in} < CL_{out}$. Microdialysis data show that the concentration profile in the brain seldom behaves as an "effect compartment" with delay in the profile due to a small k_{out} (k_{e0}). The concentration profile in the brain on the contrary follows the blood profile closely, indicating that k_{out} is often larger than k_{el} of the body. The present simulations show that the relationship of a small volume of the brain compared to the volume of the rest of the body is part of the explanation to this observation.

In conclusion, the unbound brain profiles seems to follow the blood profiles closely for more drugs than expected, even when the permeability across the BBB is low. However, the unbound concentrations in brain is much lower for many drugs studied, indicating a difference in influx and efflux clearances. The contribution of bulk flow (ECF drainage) cannot alone explain the difference. Simulations in the present paper verify that the profiles observed in microdialysis studies are compatible with active processes out of the brain, but that also active transport into the brain under certain circumstances can explain the findings.

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