Molecular Biology Reports (2020) 47:3221–3231
https://doi.org/10.1007/s11033-020-05361-2

MINI REVIEW ARTICLE

Biological barriers, and the influence of protein binding on the passage of drugs across them

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Received: 28 November 2019 / Accepted: 27 February 2020 / Published online: 5 March 2020

Abstract

Drug-protein binding plays a key role in determining the pharmacokinetics of a drug. The distribution and protein binding ability of a drug changes over a lifetime, and are important considerations during pregnancy and lactation. Although proteins are a significant fraction in plasma composition, they also exist beyond the bloodstream and bind with drugs in the skin, tissues or organs. Protein binding influences the bioavailability and distribution of active compounds, and is a limiting factor in the passage of drugs across biological membranes and barriers: drugs are often unable to cross membranes mainly due to the high molecular mass of the drug-protein complex, thus resulting in the accumulation of the active compounds and a significant reduction of their pharmacological activity. This review describes the consequences of drug-protein binding on drug transport across physiological barriers, whose role is to allow the passage of essential substances—such as nutrients or oxygen, but not of xenobiotics. The placental barrier regulates passage of xenobiotics into a fetus and protects the unborn organism. The blood–brain barrier is the most important barrier in the entire organism and the skin separates the human body from the environment.

Keywords Breast milk, Drug-protein binding, Skin barrier, Protein binding, The blood–brain barrier, The placental barrier.

Drug-protein binding

Following absorption from the gastrointestinal system or direct infusion into bloodstream, a drug can bind with plasma proteins. The main proteins responsible for the binding in plasma are human serum albumin (HSA) and alpha-1-acid glycoprotein (AAG) [1–3]. Their concentrations and functions are listed in Table 1 [4–6]. While the protein-drug complex is relatively stable, the connection between molecules is reversible: molecules can join and separate, and the equilibrium state is reached a few hours after the administration of a medicine [3].

The structure and properties of the drug determine the extent of both: plasma protein binding (PPB) and protein binding (PB) in the sense of the general process, because these concepts should be distinguished. Lipophilicity (described as logP) and acid–base properties have a significant correlation with binding [7]. Hydrophobic and acidic drugs (e.g. warfarin, ketoprofen, ibuprofen, diazepam) bind preferably to HSA, while AAG connects with the basic ones (e.g. bupivacaine, clindamycine) [6–9] which should be taken into account while setting the therapy. Binding can also increase the solubility of compounds, especially hydrophobic ones, which would otherwise not be distributed in the aqueous environment of plasma [10]. A connection with the plasma proteins protects compounds from oxidation, lowers their toxicity and increases their half-life; drugs highly bound to the plasma proteins often reveal low first pass-metabolism [10–12]. Volume of distribution depends from PB as well and is decreased for drugs highly bound in plasma or increased for those which bind in tissues [13–15]. In addition drugs with higher affinity to a binding site on a plasma protein can replace one with lower affinity and such competition can lead to an uncontrolled rise in the concentration of the free, unbound fraction of a drug [16]. This can have serious consequences for narrow therapeutic index (NTID) drugs, where the difference between therapeutic and toxic doses is minimal (e.g. cardenolides, carbamazepine, phenytoin or warfarin [17, 18]) and any changes in the concentration of unbound, active form may be poorly tolerated

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Table 1 Physicochemical properties of HSA and AAG

Plasma protein	Protein family	Concentration in plasma	Function
Human serum albumin, 65 kDa, 585 amino acids	Albumins	3.5–5 g/dL	Transport of compounds across the bloodstream (mainly hydrophobic and acidic ones), maintenance of the blood oncotic pressure, antioxidant, anticoagulant and immunomodulating properties
Alpha-1-acid glycoprotein, 44 kDa, 183 amino acids	Globulins, acute phase proteins	Depends from physiological condition	Transport of compounds across the bloodstream (mainly ones with basic properties), AAG is produced during the inflammatory state

by the organism. A sudden increase in the unbound fraction of the drug may provide a toxic effect [19]. This can lead to clinical consequences such as high risk of bleeding (warfarin) [19] or cardiac arrest (cardenolides) [20].

Level of protein binding depends on the properties of a drug but also on the surrounding environment for example, the temperature or pH. The latter can change the ionization state of the chemical compound [10, 21, 22]. The degree of plasma protein binding is governed by two variables, these being the unbound fraction of the drug in plasma ($f_{u,p}$) and the percentage of plasma protein binding (PPB%), as given below in Eqs. 1 and 2 [3]:

$$f_{u,p} = \frac{\text{unbound drug concentration in plasma}}{\text{total dose}} \quad (1)$$

$$\text{PPB\%} = \frac{\text{bound drug concentration in plasma}}{\text{total dose}} \times 100\% \quad (2)$$

An important consideration, often omitted in the literature, is that of drug-protein binding occurring outside the bloodstream. Compounds can bind with macromolecules in skin, breast milk, tissues and organs including the placenta [13, 23, 24], where they become 'stuck' and are thus prevented from reaching site of pharmacological action [23, 25]. These drugs may later pass into the plasma but in an uncontrolled way, which disturbs the dosage and the intended result of pharmacotherapy.

Transfer across biological membranes and barriers

The cell membrane is a semipermeable phospholipid bilayer, which separates cell organelles and cytoplasm from the environment. The ability of a molecule to cross the membrane depends on various factors including molecular weight, lipophilicity, ionisation state, the concentration on both sides of the barrier and protein binding [26, 27]. Low-molecular, lipid, unionised and unbound to plasma proteins molecules are reckoned as good penetrators through membranes, although extreme lipophilicity can cause accumulation in lipid environment [28, 29]. The mechanism of passive transport includes: simple diffusion (the undisturbed movement of small, lipophilic and unionized molecules across membrane) and facilitated diffusion, where specialized membrane proteins transport particles across barriers [30]. Active transport acts against the concentration gradient and as such requires energy, which is typically obtained by the hydrolysis of adenosine triphosphate (ATP). One such family of membrane proteins which actively transport drugs and other molecules across membranes is that of the ATP-binding cassette transporters (ABC transporters). They also contribute significantly to the passage of drugs through the blood–brain barrier or placenta [31]. Crossing biological barriers is a far more difficult matter. Their structure is more complex and there are additional mechanisms involved which prevent the passage of xenobiotics. Transfer across each barrier is explained in detail in the appropriate sections of this review. The most important, and the most difficult to pass, is the blood–brain barrier (BBB), which separates crucial organs from the environment.

Binding with HSA and AAG macromolecules affects the pharmacokinetic properties of pharmacologically-active compounds by decreasing their bioavailability and slowing their passage across biological membranes and barriers [32–34]; proteins themselves hardly penetrate through the cell membranes [35–37]. On the contrary new approaches in target therapy also reveal that drug binding to the protein carrier improves the effectiveness of several pharmacotherapies [38], e.g. a simple but effective mechanism was used in anti-tumour pharmacotherapy. Drug-protein conjugates penetrate into tumour circulation easily, through fenestrated capillaries, and stay trapped inside [39]. Albumin is also used as a protein carrier in commonly used drugs such as levemir, methotrexate, doxorubicin or paclitaxel [40, 41].

The blood–brain barrier

The blood–brain barrier (BBB) protects the central nervous system (CNS), which controls the whole body. Blood vessels, which are part of the BBB, are lined with

tightly-connected endothelial cells. These unique connections between the endothelial cells are called tight junctions (TJs) and adherence junctions (AJs). The BBB is also composed of a basement membrane, glial cells, pericytes and surrounding neurons [42]. The close cell connections, viz. TJs and AJs prevent the passage of molecules through the intercellular space: transport can only take place through the intracellular route, i.e. within the cells [43]. Further defence is provided by unique metabolic activity of the barrier, with enzymes such as γ-glutamyl transpeptidase (γ-GTP) or alkaline phosphatase (AP) enabling chemical decomposition of compounds which can cross the BBB from the bloodstream [42, 44]. The CNS is also protected by the diversity of its routes of xenobiotic transport mechanisms [42, 43, 45]. Of the drug efflux transporters, i.e. those of ABC transporters family P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance protein (MRP) demonstrate the highest activity in the BBB [46]. These transporters are responsible for drug distribution into the CNS and they can remove compounds which cross the barrier. Such efflux transporters have various substrates, including anti-cancer drugs, such as doxorubicin or methotrexate, antiepileptics, such as phenytoin and carbamazepine, and antidepressants, such as venlafaxine and paroxetine. While some drugs are not intended to act on the CNS, many others have to penetrate the brain to reach the main site of their activity and achieve successful therapy [46]. Drug transport across the blood–brain barrier has been widely described by Pardridge et al., with a series of articles providing a clear review of various aspects of barrier structure, the transport of drugs across it and the development of drugs for use in the CNS [47–52]. New approaches to delivering CNS drugs are also mentioned in other recent articles [53, 54].

The blood–brain barrier protects the CNS from harmful substances but its main role is to provide nutrients and oxygen, essential for the brain structures [42]. Oxygen molecules and drugs with low molecular weight and lipophilic properties can easily cross the BBB by simple diffusion [55]. Nutrition such as glucose, crucial for proper CNS function, or amino acids are carried by specific transporters (e.g. GLUT1 glucose transporter); macromolecules with high molecular mass, such as insulin, are transported in the process of endocytosis [43, 56]. Drugs can pass through the BBB by transmembrane diffusion, especially those that are lightweight or with high lipophilicity, or are carried by transporters, as in the case of glucose [55]. Two parameters (Eqs. 3 and 4) describe the amount of a drug that is passed into the CNS: log BB and log PS [57, 58]. Log BB represents the ratio between drug concentration in the CNS and plasma, while log PS indicates the permeability of certain surface; while the former is easier to obtain and more intuitive to understand, the latter is currently receiving more research attention [57, 58]:

$$\log \mathrm{BB} = \frac{\text{drug concentration in CNS}}{\text{drug concentration in plasma}} \tag{3}$$

$$\log \mathrm{PS} = \frac{\text{observed permeability across BBB } \left[{}^{\mathrm{cm}}/_{s}\right]}{\text{surface area of brain capillary endothelium } \left[{}^{cm^2}/_{g}\right]} \tag{4}$$

A number of studies have examined protein binding with drugs and their ability to cross the BBB [55, 59–61]. Albumin, like other proteins, does not readily pass through the barrier, and its drug-macromolecule complex, cannot cross. Based on this assumption, it appears that drugs which bind more readily to proteins are less able to pass into the CNS ('free drug theory' [34, 62]). This may be true for most drugs, but there are some exceptions to the rule. Several drugs which cross the BBB without difficulty, such as benzodiazepines, steroids and a few hormones, demonstrate higher concentrations in the CNS than their unbound plasma fraction would indicate [63–66]. Similar observations were made by Videbæk et al. (1999) (Table 2) [67]. De Lange and Danhof [68] collected several papers which describe highly bound drugs (oxicams [69], imipramine and desimirpamine [70], isradipine, darodipine [71]) which also penetrate the BBB in surprisingly high extent (Table 2). There are several explanations of this phenomenon. Pardridge et al. claimed that the conformation of the protein changes while interacting with capillary walls and a drug molecule is freed from a complex [64, 65, 72], Tanaka and Mizojiri ended up with similar conclusion [66]. Another idea was protein-mediated transport in which binding with protein (especially AAG) enhances the BBB penetration [62]. Several authors claimed that more permeable structure of capillary endothelium in some regions may be the reason of the increased extraction of a complex into the CNS [67, 68]. There is no doubt that protein binding has a significant role for penetrating BBB; it can either decrease the passage or affect it in the other way with mechanisms still to be discovered. Mentioned studies reveal that in vivo analyses seem to be more applicable in that case. The unique environment in the CNS or interactions between proteins and brain capillaries apparently have a high impact on the matter, therefore there is a substantial difference between in vitro and in vivo results.

The placental barrier

The placenta is a unique connection between mother and fetus. It is formed during the sixth week of pregnancy and exists until the time of birth. Its main function is to deliver nutrients and oxygen to the foetus and to remove waste and metabolites. Throughout the pregnancy, the placenta also adopts other roles: from the tenth week, it also produces

Table 2 Influence of protein binding on drug penetration into the CNS

Drug	Pharmacological activity	Plasma protein binding*	CNS penetration	Reference
Isoxicam	Non-steroidal anti-inflammatory drugs	96,5% in human serum	Increased (in the presence of HSA and AAG)	[69]
Meloxicam		99,7% in human serum	Increased (in the presence of AAG)	
Imipramine	Antidepressants	− 52% to HSA − 67% to AAG	Higher than predicted from the unbound fraction (for both proteins)	[70]
Desimipramine		− 61% to AAG	Higher than predicted from the unbound fraction (for both proteins)	
Isradipine	Calcium channel antagonists	− 91% to HSA − 92% to AAG	Higher than predicted from the unbound fraction (for both proteins)	[71]
Darodipine		− 86% to HSA − 96% to AAG	Higher than predicted from the unbound fraction (for both proteins)	
Propranolol	Beta blocker	NA**	Low, compatible with the prediction (in the presence of BSA***) Higher than predicted from the unbound fraction (in the presence of aag)	[62]
Flumazenil	GABA receptor antagonists	− 39% to HSA	Higher than predicted from the unbound fraction (HSA)	[67]
Iomazenil		− 58% to HSA	Higher than predicted from the unbound fraction (HSA)	

*Calculated from unbound fraction data available in the reference paper

**Not available

***Bovine serum albumin, used as a replacement for HSA

hormones such as chorionic gonadotropin (CG), human placental lactogen (HPL), relaxin, progesterone, testosterone, oestrogens etc. and it manifests metabolic activity [73, 74]. Inside the placenta the blood vessels from a mother and a child are tangled together but the blood itself does not mix; despite this, sufficient exchange of substances is maintained between the organisms [73]. Due to its high permeability, the placenta acts more as a filter than an actual barrier [75]. Bacterial cells are retained within the placenta as are macromolecules, such as insulin or heparin, and immunoglobulins, except IgG. Most drugs pass through the placental barrier, including barbiturates, antibiotics, sulphonamides and alcohol [75]. Small molecules cross the barrier by simple diffusion, while drugs also cross by facilitated diffusion or active transport [75] or by endocytosis [73, 76–78]. It is assumed that the penetration of drugs through the placenta is limited mainly by protein binding rather than lipophilicity [79]. A significant role in the active transport of drugs is played by the ATP-binding cassette transporters, with the main ones being glycoprotein P and breast cancer resistance protein. They can either transport drug molecules to the fetal side or return them into maternal circulation; of these, the latter function is assumed to be more important, and plays a significant role in forming the placental barrier [77].

During pregnancy, it is difficult to avoid pharmacotherapy, and drug usage has increased in recent years. Drugs are administered in the treatment of chronic diseases such as epilepsy, diabetes, hypertension or they are prescribed temporally to treat infections such as the common cold. Additionally pregnant women often take over-the-counter drugs and dietary supplements, without medical advice [80, 81]. The amount of a drug which crosses the placental barrier is dependent on various factors: its physicochemical properties, pharmacokinetics, the concentration gradient on both sides of the barrier, the differences in pH in between maternal and foetal plasma and the levels of protein binding in both organisms [80, 81]. Protein binding is considered the important property in determining drug transport through the placenta, influencing both the speed and the extent of this process [16, 74].

The distribution of a drug between mother and child is limited also by the concentration of main plasma proteins. These change continually over the course of pregnancy: while the concentration of foetal albumin (alpha-fetoprotein, AFP) is lower than the maternal HSA level during the initial stages of pregnancy, it can be up to 20% higher than maternal HSA at childbirth [16]. The amount of foetal alpha-1-acid glycoprotein also increases with the development of the foetus; however, it never exceeds adult levels, remaining about 30–40% lower [16]. There are also differences in affinities to protein binding sites, with AFP attracting fewer molecules than HSA in adult plasma [82]. Protein binding can also occur in both maternal and foetal tissues; drug molecules can also form a repository in the placenta, from which it can be released in uncontrolled way into the maternal or foetal plasma [16].

In vitro experiments with propofol using a human placenta model by He et al. [79, 83] found propofol clearance to correlate with the concentration of fetal albumin. It appears that the potential to cross into the placenta is significantly dependent on binding with alpha-fetoprotein: an increase of alpha-fetoprotein concentration results in greater drug penetration. It was also found that infiltration across the placental barrier diminishes as the concentration of maternal HSA rises. Elsewhere, [84] it was found that HSA has a great influence on citalopram and fluoxetine placental transport, with its presence in the perfusion solute increased the degree of penetration; this effect was correlated with the affinity of the drugs to HSA: the passage of fluoxetine (PPB% = 94%) was significantly lower than that of citalopram (PPB% = 50%).

The placenta is considered a very weak barrier against xenobiotics and most of the administered drugs can easily cross it. Plasma protein binding appears to affect this process because it significantly limits placental transit, but alpha-fetoprotein concentration increase which can enhance the passage is also an important matter. The accumulation of drugs in the placenta is still underestimated and it needs to be studied in detail to get a clearer picture of the processes that can affect fetal safety during pharmacotherapy.

Skin barrier

The skin is the largest human organ, and one which separates the internal environment from the surroundings and protects it from various pathogens. As a barrier, the skin also prevents the penetration of many chemical compounds. This poses a challenge for the design of dermatological preparations, which are quite common in modern pharmacotherapy, mainly due to their easy and convenient application and lack of side effects typical for the oral administration. Dermatological application can also enhance the systemic activity of a drug [85]. It has previously been assumed that most of the administered drug particles are absorbed into the skin circulation, thus allowing them to pass into the bloodstream, and that the process was regulated by the skin structure and condition, the structure of the drug and the type of pharmaceutical formulation [85, 86]. However, later studies suggest that the most important factors determining skin penetration are the structure and properties of the drug [85]. The permeability of the skin varies across its surface in response to changes in its structure, for example, variation in the numbers of follicles or the thickness of the stratum corneum [87].

Externally administered drugs can bind with the proteins within the skin layers, which can be desirable if only local action is intended: the drug will accumulate at its site of activity and will not cause any adverse systemic effects. However, in the case of transdermal drugs such skin protein binding will disturb their flow into the circulation, slow the passage through the skin and reduce the overall amount of active molecules in the system. Previously, it was found that highly protein binding drugs achieved lower concentration in plasma and the time of skin penetration was longer [88]. A 2008 study [89] examining the different pharmacodynamics of tacrolimus and pimecrolimus with regard to their ability to penetrate the skin found that pimecrolimus is more likely to bind non-specifically with various skin protein than tacrolimus, thus yielding a lower systemic concentration (Table 3). Similarly, benzocaine has also been found to accumulate in the skin through non-specific binding (Table 3) [90].

These results suggest that protein binding in the skin should be carefully studied in case of dermatological formulations, especially for highly protein binding drugs. Albumin is present in the skin [91] so the correlation between binding to HSA in plasma and skin could be a useful tool in pharmaceutical design. Nowadays, only the process of skin sensitisation is widely examined, which is supposed to be the result of non-covalent, reversible binding of various compound with skin proteins, including albumin [92, 93].

Drug penetration into breast milk

During lactation, similarly to pregnancy, it can be difficult to avoid the use of any medicines. Many women abandon breastfeeding when they take drugs, but often unnecessarily. The penetration of most xenobiotics into milk is quite low and only a fraction is typically ingested by an infant [94, 95]. The amount of a drug in breast milk is estimated using the M/P ratio for a particular drug (Eq. 5): this represents the ratio between concentration of the drug in milk and in maternal plasma:

Table 3 Influence of protein binding on skin penetration

Drug	Pharmacological activity	Protein binding in skin	Skin permeability	Reference
Pimecrolimus	Calcineurin inhibitors	High, non-specific binding to human skin proteins	Lower penetration than in the case of tacrolimus	[89]
Tacrolimus		Low, non-specific binding to human skin proteins	–	
Benzocaine	Local anaesthetic	Accumulation of significant amount of benzocaine in skin	Low penetration	[90]

$$M/P = \frac{\text{drug concentration in milk}}{\text{drug concentration in plasma}} \quad (5)$$

This parameter should be calculated for each drug individually and can be obtained from clinical studies, observations of single, medical cases or derived mathematically, using chemometric methods [96–101]. Drugs with M/P value lower than 1 are considered as safe for breast-feeding child.

Breast milk is regarded as the best nourishment for a newborn infant, and for first six months of life, it can be its only food. Milk is produced in the mammary glands by specialised cells called lactocytes [102]. It is composed of a mixture of water and carbohydrates, proteins, lipids, vitamins and various other nutrients [103], with the composition changing over the course of lactation [104, 105]. During the first stage of lactation, breast milk, colostrum, is composed mainly of structural proteins and proteins which support the immune system e.g. lactoferrin or immunoglobulins [106, 107]. This is later replaced by transitional milk, which has higher levels of carbohydrates and lipids and it is more nutritious than colostrum. Mature milk is produced around the third week after birth, and it consists of around 7% carbohydrates, 4% lipids and less than 1% proteins [102, 106, 108]. This is later replaced by transitional milk, which has higher levels of carbohydrates and lipids and it is more nutritious than colostrum. Mature milk is produced around the third week after birth, and it consists of around 7% carbohydrates, 4% lipids and less than 1% proteins [109].

Drugs mostly penetrate into breast milk by simple diffusion along a concentration gradient. This process is also limited by various factors connected with the compound structure: molecular weight, lipophilicity, protein binding or pKa [94, 110]. The pKa of a drug plays an important role on its accumulation in milk: the mean pH of breast milk ranges from 7.1–7.2 while that of plasma is around 7.4 [102, 105]. Weak bases become ionized in breast milk, trapping them inside the mammary gland and preventing their return to maternal plasma [111]. In addition, drugs with high lipophilicity can also accumulate in the lipid phase of breast milk, and while protein binding can prevent the passage of molecules into milk, drugs also bind with the breast milk proteins themselves [112]. The composition of the protein phase consists of alpha-S1, alpha-S2, beta- and kappa-caseins, alpha-lactoalbumin, beta-lactoglobulin, plasma albumin and lactoferrin, as well as immunoglobulins A, M, G and lysozyme and alpha-1-acid glycoprotein [104, 113]. However, drug binding is typically weaker in breast milk than in plasma [111].

Drug transfer into breast milk is still a difficult subject for in vivo study. Although clinical studies have been performed, they are usually based on very small groups of subjects or describe individual cases. Short-term use of drugs, during infection for example, seems to be less problematic than in the case of long-term pharmacotherapy. Women suffering from chronic conditions such as multiple sclerosis, epilepsy or psychiatric disorders, or those undergoing anticancer therapy, often want to maintain breast-feeding. A review by Constantinescu et al. [114] examined the usage of various immunosuppressive drugs, including azathioprine, belatacept, corticosteroids, cyclosporine A, everolimus, sirolimus and tacrolimus, during lactation. A study of methylprednisolone levels in the breast milk of two lactating women, one of them after renal transplantation and the other with multiple sclerosis [115, 116] found that methylprednisolone passes poorly into milk, which could be related with its high PPB%, estimated to be around 79% (Table 4) [116].

A 2013 study of antiepileptic drugs by Davanzo et al. [117] reviewed a body of pharmacokinetic and clinical data, including relevant infant dose (RID), and toxicity guidelines taken from LactMed [118] and Hale [119]. Older-generation drugs such as carbamazepine, phenobarbital, phenytoin and valproic acid were found to be relatively safe, even phenobarbital, which weakly binds with plasma proteins in maternal plasma (20–45% [120]). The overall conclusion was that neither pharmacokinetic or literature toxicity parameters are good predictors of the drug penetration into breast milk. The penetration of cisplatin across the placenta [121] and into breast milk (Table 4) [121, 122] was also studied. The drug was found to demonstrate poor penetration into milk as its platinum ion binds strongly with plasma proteins [120, 122]. However, cisplatin is contraindicated during lactation, probably due to the fact that that it accumulates during repeated dosage.

Postpartum depression or anxiety also requires a long-term treatment. SSRIs (selective serotonin reuptake inhibitors) are believed to be the safest drugs for lactating women because their high PPB% values, among other factors, prevent them from crossing readily into milk (Table 4) [123]. One exception is paroxetine, as it has been linked with an increased risk of heart dysfunction [124]. A detailed reviews about CNS drugs usage during lactation by Eberhard-Gran et al. and by Weissman et al. [125, 126]. They provide data regarding drug secretion into breast milk and recommendations for use. The latter study also points out the negative correlation between PB and M/P values [125]. Further information about the use of antidepressants is also given in a review by Lanza di Scalea and Wisner [127].

In most of the cases described, where the excretion of the drug into milk is very low, one of the main reasons mentioned is high plasma protein binding. This may indicate that milk penetration may be the most PPB dependent of all the barriers described in this review. Another issue to consider is milk protein binding, which further reduces the amount of medicine an infant ingests. Experts claim that breastfeeding should not be interrupted during pharmacotherapy unless it

Table 4 Penetration into breast milk of highly protein bound drugs

Drug	Pharmacological activity	Plasma protein binding	Penetration into breast milk	Reference
Methylprednisolone	Corticosteroid	75–82%*	Poor penetration, average infant exposure was 0,188 mg/kg/day with maternal dose of 1000 mg/day	[116]
Cisplatin	Chemotherapeutic agent	90%*	Cisplatin was undetectable in breast milk, maternal dose was 70 mg weekly (repeated in 4 cycles)	[122]
Citalopram	Selective serotonin reuptake inhibitors (SSRI)	80%**	Poor penetration, citalopram average milk level was 157 mcg/l with average maternal dose of 29 mg/day	[125]
Fluoxetine	SSRI	94%**	Poor penetration, fluoxetine average milk level was 76 mcg/l with average maternal dose of 28 mg/day	[125]
Sertraline	SSRI	98–99%**	Poor penetration, sertraline average milk level was 45 mcg/l with average maternal dose of 83 mg/day	[125]

*According to the reference paper

**According to DrugBank database [120]

is necessary, which seems to be a reasonable solution. However, there should be sufficient evidence that the medicine is safe for breastfed infants or wouldn't interrupt the lactation.

Summary

Drug-protein binding has a significant influence on the pharmacokinetic properties of most compounds. It can limit the bioavailability of active compounds by controlling their passage through biological membranes; however, binding to plasma proteins allows hydrophobic drugs to be transported in the aqueous environment of the human organism. The drug-protein complex is less likely to cross the placental barrier or to enter breast milk, which decreases the negative effect of medicines on breastfeeding infants; however, some drugs can accumulate in placental tissues or in milk by binding with proteins in these regions, and upon their later release, enter the foetus or infant in uncontrolled way. Passage through the blood–brain barrier is more complicated by mechanisms which protect the central nervous system, such as active efflux and the use of strong protein binding mechanisms. Additional unknown mechanisms that lead to the penetration of several protein-bounded drugs make this matter even more complex. Skin penetration is an important issue for transdermal drugs because they have a strong impact on their bioavailability and protein-binding interacts with this process.

Protein binding is relatively simple to study in vitro, but its effect on crossing biological barriers in a living organism could be difficult to grasp with these methods. This is probably due to the complexity of the entire barrier-crossing process and additional side-effects that simply cannot be obtained in the laboratory.

Acknowledgements This work was supported by an internal grant of the Medical University of Lodz no. 502–34-106.

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest, financial or otherwise.

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