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Minimizing Drug Exposure in the CNS while Maintaining Good Oral Absorption

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ABSTRACT: In some drug discovery approaches, it is advantageous to restrict the access of compounds to the CNS to minimize the risk of side effects. By choosing appropriate physicochemical properties and building in the ability to act as substrates for active efflux transporters, it is possible to achieve CNS restriction and still retain sufficient absorption through the intestinal epithelium to retain good oral bioavailability. Potential risks in employing this approach are considered.

For drugs that are required to act at targets outside of the central nervous system (CNS), it may be advantageous to minimize drug exposure in the CNS. Many instances exist where side effects have been attributed to on- or off-target actions of a drug in the CNS that lead to issues of safety and tolerability. Furthermore, in the research phase, the ability to test a novel pharmacological mechanism could be limited by such side effects.

The first generation of histamine H1 antagonists used for the treatment of allergic reactions serves as an example, whereby diphenhydramine, while effective as an antiallergic agent, also caused somnolence and other CNS side effects as a result of engagement with H1 receptors in the brain. The second generation agents, for example, cetirizine, had reduced side effects with reduced somnolence at therapeutic doses, while the third generation, including fexofenadine, were free of sedation at doses higher than those used for treatment of allergic reactions. This progression resulted from increasing CNS restriction of these agents, thereby increasing their peripheral H1 selectivity.[1] Other examples include antimuscarinic agents used for the treatment of overactive bladder, which act by binding to muscarinic receptors in the bladder detrusor muscle. Effects such as cognitive impairment, particularly in elderly patients, have been reported for agents such as oxybutynin, which penetrate the CNS readily and are thus able to interact with centrally located muscarinic receptors. Other agents such as darifenacin and 5-hydroxymethyltolterodine (active metabolite of fesoterodine) are not associated with CNS side effects and are largely excluded from the CNS.[2]

Therefore, a general approach that may be advantageous when considering peripherally located drug targets is to restrict the access of compounds to the CNS while maintaining appropriate exposure in peripheral tissues. This may apply particularly when the peripheral therapeutic target is known to be present in the CNS but whose engagement there is not required for desired pharmacological activity. However, it also represents a general means of minimizing risk of unexpected off-target effects in the CNS, thereby increasing therapeutic index.

The properties of the brain capillary vascular endothelium that supply blood to the CNS provide a barrier to the free exchange of blood-borne solutes. Efficient tight junctions between adjacent brain vascular endothelial cells (BVECs) restrict passage of solutes between adjacent cells (paracellular movement) so that to traverse the endothelium, compounds have to cross the BVEC plasma membrane (transcellular movement). Hence, the physicochemical properties of a brain penetrant compound need to be compatible with the ability to diffuse passively across the plasma membrane and/or participate in active uptake. In addition, ATP-dependent transporter proteins such as P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), expressed in the BVEC apical membrane, are capable of ejecting substrate compounds from the cell. These features of the BVECs constituting the blood−brain barrier (BBB) offer opportunities to design compounds with properties that exploit the requirement for transcellular movement and presence of transporter proteins, to achieve the goal of restricted CNS penetration.

However, the properties of orally administered compounds should also be compatible with those required for absorption across the intestinal epithelium that acts as a permeability barrier in the gastrointestinal tract. Molecular weight (MW) < 500, polar surface area (PSA) < 140, and <10 rotatable bonds have been associated with good oral absorption, while MW < 450 and PSA < 70 have been indicated as requirements for good CNS penetration.[3,4] Hence, to favor restriction from the CNS while allowing good absorption in the gastrointestinal tract may point to an area of compatibility of MW of 450−500 and PSA of 70−140. Like the BVECs, the intestinal epithelium contains several efflux transporter proteins, including P-gp and BCRP, expressed on the apical membrane of intestinal epithelial cells (enterocytes) (Figure 1).

P-gp and BCRP are expressed at comparable levels in human brain capillaries, and in mouse gene knockout studies, it has been shown that they may both contribute to exclusion of substrates from the brain.[5] This suggests that design of compounds that act as substrates for both P-gp and BCRP may maximize their CNS restriction. Indeed, P-gp and BCRP display considerable overlap in their substrates (e.g., imatinib is a substrate of both), although some compounds are exclusively substrates of one or the other (e.g., cetirizine is P-gp only). Increasing MW and PSA increases the likelihood of compounds to act as substrates of P-gp. Additional features include

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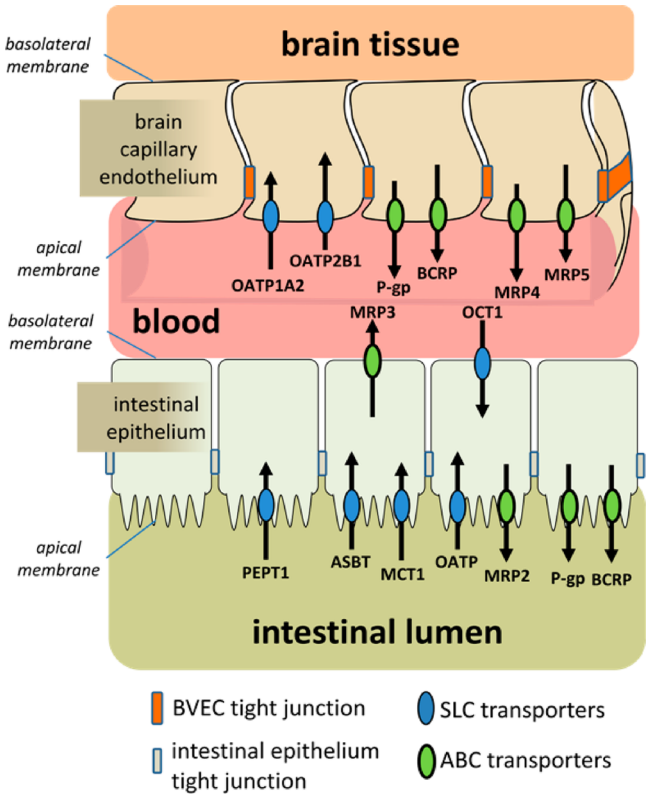

Figure 1. Schematic diagram of the distribution of transporter proteins in the intestinal epithelium and brain vascular endothelium.

possession of hydrogen bond acceptors and modest ionization potential (acid pK_a > 4; basic pK_a < 8). These features broadly align with those identified for balancing CNS restriction and intestinal absorption.

Targeting efflux transporters as part of a drug discovery strategy may suggest a conundrum if efflux transporter expression in enterocytes renders CNS restriction and good oral absorption incompatible. However, this could be a misconception as there are several instances of drugs that are substrates of P-gp and BCRP, CNS restricted, and possess good oral bioavailability. Considering drug doses commonly prescribed for clinical use (10−500 mg) and the resulting range of drug concentrations likely to exist in the gastrointestinal lumen following an oral dose (assuming dissolution in ∼250 mL), P-gp is often likely to be saturated by drug substrates in the gut, given that the K_m for P-gp is usually in the range 1−100 μM.[6] In contrast, systemic unbound drug concentrations are likely to be in the submicromolar range and hence unlikely to be at concentrations sufficient to saturate transporters in the BVECs. For example, the antitumor agent imatinib is a P-gp and BCRP substrate, with limited brain exposure and high oral bioavailability.[7] The unbound plasma C_{max} of imatinib following a dose of 400 mg is approximately 250 nM and is unlikely to saturate P-gp or BCRP at the BBB. The antiviral protease inhibitors ritonavir and indinavir serve as other examples of CNS restricted P-gp substrates having high (60−78%) oral bioavailability.[5]

Steady state brain concentrations of a compound result from the net effect of passive and active movements across the BBB, so strategies designed to exclude compounds from the brain could focus on active and passive processes. Maintaining very low passive permeability such that equilibrium between blood and brain tissue is not allowed to occur may have the drawback of impairing intestinal absorption. While, in this case, a nonoral dose route could be explored, oral administration is usually the preferred dose route. In our opinion, the strategy most likely to deliver CNS restriction with good oral absorption is to maintain an efflux rate at the BBB that greatly exceeds influx rate, whereby efflux is mediated by P-gp and BCRP against a background of low-moderate passive permeability. We have utilized this approach successfully at Pfizer to design CNS restricted orally bioavailable ligands.[5] A series of CNS restricted histamine H3 antagonists was designed to minimize clinical adverse events such as insomnia that would otherwise be observed. Optimizing PSA, reducing passive permeability, and introduction of activity as P-gp and BCRP substrates led to demonstration of CNS restriction in *in vivo* tissue partition experiments in rat. Good oral bioavailability (>50%) was maintained in rat while brain receptor occupancy data confirmed that CNS restriction was maintained over 7 days of dosing, and electroencephalography data demonstrated the desired TI for efficacy over insomnia.

While the H3 antagonist approach dealt with an extracellular target, the design of CNS-restricted drug candidates for intracellular drug targets must incorporate sufficient cellular permeability to reach the site of action, yet maintain low BBB penetration. Therefore, the use of cell-based primary screens together with timely *in vivo* efficacy and CNS restriction experiments is vital to ensure that candidate compounds combine efficacy and CNS restriction. By application of this approach, we have developed CNS restricted ligands (rat unbound brain:plasma ratio 0.015) for an intracellular target having high cellular potencies ($IC_{50} \leq 20$ nM) combined with good oral absorption, as demonstrated by linear pharmacokinetics over a wide dose range (0.25−1000 mg/kg) in preclinical rodent safety studies.

There are identifiable risks associated with building in P-gp and BCRP active efflux to a drug approach, some of which can be addressed by evaluation of clinical data. A drug−drug interaction (DDI), potentially leading to unwanted CNS penetration, could arise if a P-gp substrate is concomitantly administered with a P-gp inhibitor. However, considering the free drug exposures expected at the BBB, only a very potent P-gp inhibitor could be expected to elicit a significant effect. DDI associated with absorption could be expected, given P-gp expression along the intestinal epithelium. Nevertheless, clinical data obtained with the P-gp substrate digoxin suggest that in the majority of cases when a P-gp inhibitor and substrate are coadministered, the digoxin AUC change was less than 2-fold.[8] It is also possible that P-gp substrates will display nonlinear dose versus exposure relationships, depending on their Km for P-gp. However, as metabolism by CYP3A4, and hence first-pass extraction, often accompany P-gp affinity,[6] it may be difficult to assess the contribution of each enzyme to any nonlinearity observed. Presently, our ability to accurately predict absorption of P-gp and BCRP substrates is limited until more quantitative information on intestinal transporter expression become available. A number of polymorphisms of P-gp and BCRP are present in the human population that could lead to interpatient variability. For instance, the MDR1 gene single nucleotide polymorphism C3435T is linked to decreased duodenal P-gp expression and modest increases in digoxin exposure. Similarly, changes in BBB permeability and P-gp expression may occur with aging and in certain disease states that may alter the degree of CNS restriction. Finally, a significant concern in compound

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selection for clinical studies may be whether CNS restriction measured preclinically accurately predicts that which occurs in human. Many preclinical evaluations are conducted in rodents whose transporter expression profile at the BBB differs from human. Furthermore, a number of recent studies indicate that the degree of CNS restriction can exhibit species differences whereby higher primate species, including human, may display significantly higher CNS exposure than in rodents.[5]

In conclusion, designing in CNS restriction can be used to improve drug safety. Targeting the efflux transporters P-gp and BCRP alongside modest passive permeability can confer significant CNS restriction while retaining good oral bioavailability, cell penetration, and pharmacological activity. However, there are identifiable risks with this strategy that may be clarified as further clinical data emerge.

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Notes

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