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BEYOND THE BLOOD–BRAIN BARRIER: MEDICINAL CHEMISTRY STRATEGIES FOR BRAIN-TARGETED PRODRUG DESIGN

Omkar Rai[1]*, Soma Sekhar Pulamarasetti[1], Rupesh Soni[1], Soumik Das[2]

[1] Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001)

[2] Department of Pharmacy / Central University of Rajasthan (CURAJ), NH-8, Bandarsindri, Ajmer District, Rajasthan, India (PIN: 305817)

Abstract:

The blood–brain barrier (BBB) is a highly selective neurovascular interface that protects the central nervous system (CNS), but also limits therapeutic access to the brain. In medicinal chemistry, the prodrug design provides a reversible approach to change polarity, ionization, lipophilicity, transporter recognition and metabolic stability to allow delivery of a pharmacologically active parent drug to the CNS and its regeneration upon crossing the barrier. This extended review deals with the chemical rationale of brain-directed prodrugs, emphasizing passive-diffusion enhancement, masking of ionizable groups, transporter-mediated uptake, receptor-mediated delivery, redox chemical delivery systems, intracellular trapping and self-immolative or cascade activation. The roles of P-glycoprotein and associated efflux systems, disease-state alterations in the BBB, in vitro and in vivo evaluation, quantitative pharmacokinetics/pharmacodynamics and computational approaches are also reviewed. Comparative tables summarize design variables, representative historical and contemporary strategies, activation mechanisms, experimental models and translational risks. Original schematic figures and literature-mapping charts are provided to make the structure property-mechanism relationships visually explicit. The primary takeaway is that BBB penetration alone is not enough to define successful brain targeting. The prodrug must remain sufficiently stable in systemic compartments, cross the relevant brain barrier, undergo productive activation in the intended tissue or cell type, and generate adequate free parent-drug exposure while minimizing peripheral toxicity. Recent literature reinforces a shift from generic lipophilicity enhancement toward mechanism-based, multi-parameter and site-selective prodrug engineering.

Keywords: *Blood–brain barrier; CNS drug delivery; brain-targeted prodrug; medicinal chemistry; LAT1; GLUT1; transporter-mediated delivery; efflux transporters; chemical delivery system; redox targeting; bioactivation; self-immolative linker; neuropharmacology; PK/PD; CNS drug discovery.*

Corresponding author:

Omkar Rai,

Faculty of Pharmacy, B. R. Nahata College of Pharmacy,

Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001)

Mobile: +91 9792279812

Email Id: *omkarrai274304@gmail.com*

QR CODE

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1. INTRODUCTION:

The BBB is the major pharmacological gatekeeper between the systemic circulation and brain parenchyma. Tight junctions between specialized brain endothelial cells, low endothelial vesicular trafficking, a metabolically active endothelial layer, pericytes, astrocytes and polarized influx/efflux transporters jointly produce a barrier that is dynamic rather than merely anatomical [1–10]. Classical CNS drug-development literature has repeatedly shown that inadequate brain exposure can terminate otherwise potent candidates before target engagement is ever tested in the disease-relevant tissue [1–3, 9, 16].

The medicinal-chemistry response has traditionally focused on increasing passive membrane permeability. This can involve reducing exposed polar surface area, changing ionization, adding lipophilic substituents, masking hydrogen-bonding groups or creating ester/carbonate/carbamate derivatives. Yet simple lipophilicity enhancement is not universally successful because excessive hydrophobicity may increase nonspecific binding, peripheral distribution, metabolic clearance or efflux recognition [11, 18, 24, 55]. The prodrug strategy therefore represents a more controlled way to transiently change molecular properties and restore the parent drug after transport.

Brain-targeted prodrugs introduce a second objective beyond permeability, namely spatially selective bioactivation. A prodrug that is rapidly converted in plasma or liver may increase systemic exposure without increasing active drug in brain. Conversely, a derivative with enough peripheral stability but more efficient activation upon entry into the CNS can increase the brain-to-plasma exposure ratio. This principle, initially articulated in early chemical-delivery-system work and revisited in recent reviews, remains central to modern CNS prodrug design [11, 12, 29–51, 81, 82].

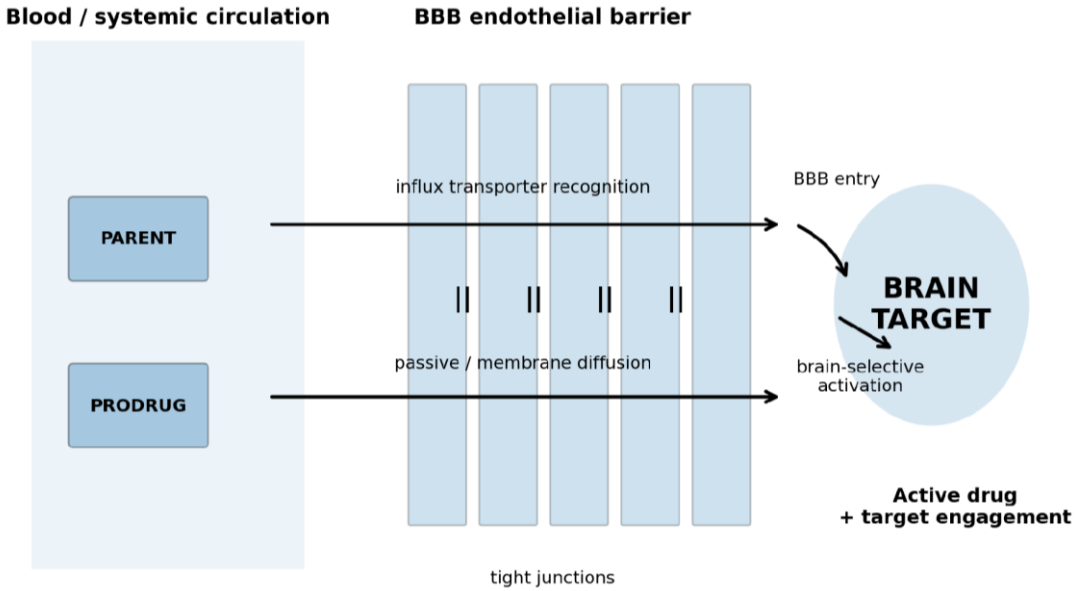

Figure 1 Schematic prepared for this review. The design of brain targeted prodrugs is considered to involve a series of processes, including systemic stability, entry to the brain, selective activation in the brain, retention, and target engagement. The figure brings together the concepts of passive diffusion and transporter-mediated entry discussed in refs. [1–18, 52–80].

2. Biological Basis of Brain Drug Penetration

2.1 Structural components of the BBB

The brain capillary endothelial cells are the major cellular interface for the BBB. Their tight junctions block paracellular transport and polarized membrane domains govern transporter-mediated influx and efflux. Within the neurovascular unit, pericytes and astrocytic end-feet serve as supporting cells for barrier integrity and signaling. These properties are of direct relevance to medicinal chemistry as the effective permeability of a molecule depends on both membrane partitioning and interactions with barrier proteins [3, 4, 40–54].

2.2 Passive diffusion

Passive entry to the BBB is favored by relatively small, moderately lipophilic and weakly ionized molecules. In the historic analyzes, molecular mass, lipophilicity and ionization were used as practical screening variables, but these are now regarded as interacting descriptors, rather than universal thresholds [9, 10, 40, 55]. A molecule may be lipophilic but have low brain exposure because of active efflux or high plasma protein binding. In contrast, an endogenous transporter can efficiently allow entry of a polar molecule.

2.3 Carrier-mediated entry

Among the most attractive rational strategies for converting a physicochemically unsuitable molecule into a CNS-compatible prodrug is carrier-mediated transport. Substrate-like chemical motifs are recognized by endogenous solute carriers such as LAT1 and glucose transport systems. Several studies have shown that conjugation with amino acids can affect the disposition of drug-like molecules and provide a mechanistic route across BBB [52–75].

2.4 Efflux transporters

P-glycoprotein (ABCB1), BCRP (ABCG2) and related transport systems can limit net brain exposure by returning drugs from endothelial cells to blood. Efflux thus can counteract improvements in lipophilicity or passive permeability [70–80]. This liability can be overcome by a brain-targeted prodrug, by minimizing transporter recognition, by taking advantage of a favorable uptake/efflux ratio, or by designing the activation such that the active product is retained after entry.

Figure 2. Principal routes for brain delivery of small-molecule prodrugs

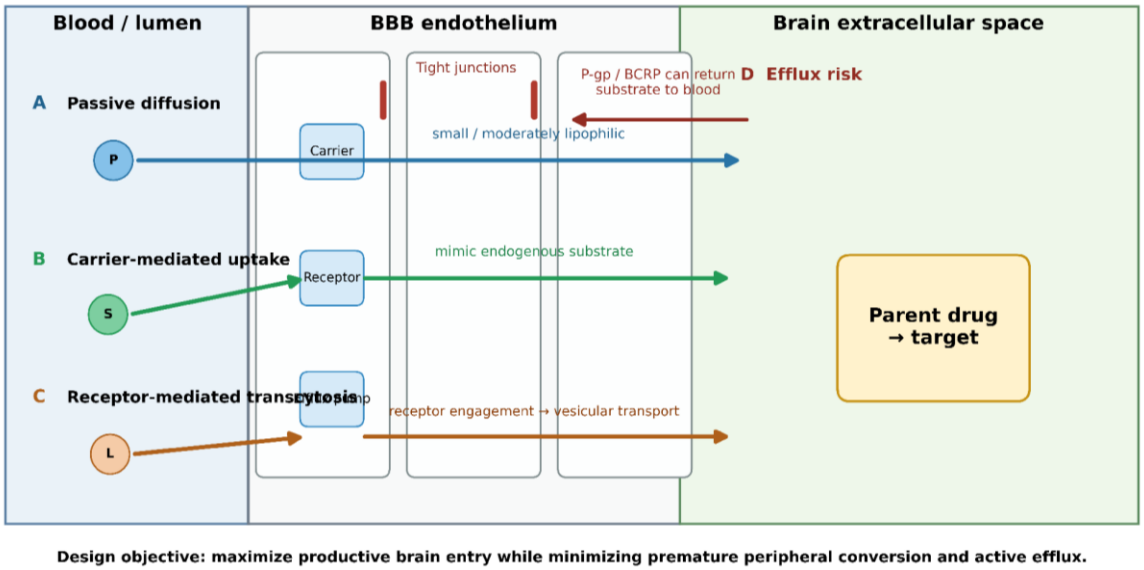

Figure 2. Schematic of the major routes of small-molecule prodrug design to target the brain (original). The diagram highlights the competition between influx and efflux and the importance of post-entry bioactivation. Concepts supported by refs. [52–80].

3. Prodrug Concept in CNS Drug Design

A prodrug is a bioreversible derivative that undergoes chemical or enzymatic conversion to release a pharmacologically active parent. In CNS applications, this concept is useful when the parent drug has an unfavorable physicochemical or transport profile, such as excessive polarity, poor membrane partitioning, low oral absorption, or susceptibility to rapid metabolism [18–27].

Brain-targeted prodrugs add a directional requirement: the prodrug should preferably reach brain tissue before substantial activation, or it should be activated more strongly in the CNS than in peripheral tissues. The design can therefore be represented as a kinetic competition among absorption, distribution, barrier transport, peripheral conversion, brain conversion, parent-drug elimination and pharmacodynamic action [11, 29–55, 81].

4. Major Medicinal Chemistry Strategies for Brain-Targeted Prodrugs

4.1 Lipophilicity enhancement and masking of polar groups

Esterification and related masking reactions can reduce polarity and temporarily suppress ionization of carboxylates or alcohols. The strategy is synthetically accessible and can generate series of promoieties whose stability is tuned through steric and electronic substitution. The key failure mode is premature systemic hydrolysis. Early CNS prodrug work showed that high plasma esterase activity can convert a candidate before it ever reaches the brain [11, 29, 84].

4.2 Redox chemical delivery systems

Redox chemical delivery systems (CDS) exploit reversible oxidation-state changes to produce an intermediate that can cross biological membranes and then become trapped after oxidation within the

brain. This concept was developed extensively for zidovudine, ganciclovir, estradiol and other agents and is still a landmark example of chemical targeting rather than mere permeability enhancement [34–45].

4.3 Carrier-mediated prodrugs

Transporter targeting turns an obstacle into a recognition event. LAT1 is particularly attractive because it is highly expressed at the BBB and generally transports large neutral amino acids . Examples of modulation of structure to achieve substrate-like properties by medicinal chemists include L-tyrosine-conjugates and other amino-acid conjugates [56–69]. The major challenge is to get high enough transporter affinity without excessive peripheral uptake and with release of the parent drug inside the BBB.

4.4 Glucose transporter and nutrient-mimetic strategies

Strategies that target GLUT1 engage a physiologically relevant BBB influx pathway, using either glucose-like or glycosylated motifs. Proof of concept examples have been studied using dopamine and chlorambucil derivatives [61, 70-74]. Given the systemic expression of nutrient transporters, selectivity is a function of the balance between transporter recognition, BBB abundance, distribution and intracellular release kinetics.

4.5 Receptor-mediated delivery

Although receptor-mediated transcytosis is often discussed for macromolecules and nanoparticles, it is just as conceptually relevant for prodrug design: the delivery moiety is a molecular address label and a trigger or linker determines release. Two prominent examples are the transferrin-receptor and insulin-receptor systems in the broader CNS-delivery literature [88–91 and related BBB-targeting work]. For small-molecule prodrugs, receptor engagement must be sufficient to influence trafficking but not so high as to result in unacceptable systemic pharmacology.

4.6 Intracellular trapping and cascade activation

A modern prodrug can be designed such that the first metabolic event reveals a latent functionality that can then undergo intramolecular cyclization fragmentation or a self-immolative cascade . This results in rapid release of the active parent drug. This architecture separates BBB entry from drug release and can, in principle, transform a diffusible prodrug into an intracellularly retained active species. Recent literature emphasizes that the activation mechanism and tissue selectivity are as important design considerations as permeability [81].

4.7 Codrugs and dual-function prodrugs

Codrug approaches connect two pharmacophores or a drug with an absorption/transport motif. A classic example is an L-dopa–entacapone codrug intended to improve the therapeutic use of L-dopa [86]. Such systems may offer combined pharmacology but also increase molecular size and complicate metabolic characterization.

5. Physicochemical Design Space

Table 1. Physicochemical design space.

Parameter	Design objective	Potential benefit	Main risk
Lipophilicity (logP/logD)	Moderate, context-dependent increase	Improves membrane partitioning	Nonspecific binding, peripheral distribution, metabolic burden
pKa / ionization	Reduce permanent charge; tune neutral fraction	Improves BBB diffusion	Loss of target binding or chemical instability
Hydrogen-bonding	Temporarily mask exposed donors/acceptors	Reduces desolvation penalty	May reduce aqueous solubility
Polar surface area	Lower exposed PSA when diffusion is intended	Can increase passive permeability	Over-masking may impair activation or transporter binding
Molecular size	Keep within feasible CNS design space	Supports passive diffusion	Large size can reduce permeability and raise complexity
Transporter affinity	Selective substrate-like recognition	Enables polar prodrug entry	Peripheral transporter uptake / saturation
Efflux recognition	Minimize or overcome	Improves net brain exposure	May be structure-dependent and hard to predict

Parameter	Design objective	Potential benefit	Main risk
Systemic stability	Sufficient for BBB delivery	Prevents premature release	Excessive stability causes poor activation
Brain activation	Higher than peripheral activation when possible	Improves brain selectivity	Requires tissue-specific enzyme/reaction knowledge

6. Representative Brain-Targeted Prodrug and Chemical-Delivery Examples

Table 2. Representative brain-targeted prodrug and chemical-delivery examples.

Parent / payload	Prodrug or chemical strategy	Targeting logic	Key lesson
Chlorambucil	Lipophilic ester derivatives	Increase lipophilicity for CNS access	Higher lipophilicity alone does not guarantee selective brain activation [32,33]
Zidovudine (AZT)	Redox chemical delivery system	Brain trapping after oxidative conversion	Illustrates reversible redox targeting and tissue retention [38,39,50]
Ganciclovir	Redox targeting	CNS-directed chemical delivery	Demonstrates feasibility of brain-selective chemical delivery [40]
Estradiol	Redox CNS-directed system	Sustained brain-directed exposure	Shows that local trapping can reshape pharmacodynamics [43–45]
Benzylpenicillin	Dihydropyridine / redox derivatives	Transient BBB-permeable state	Early proof-of-concept for chemical targeting [41,42]
L-DOPA / dopamine	Glycosyl and nutrient-mimetic derivatives	GLUT1-related uptake	Transporter engagement can compensate for polarity [61,73,74]
4-Chlorokynurenine	Transport / facilitated entry	Conversion to active 7-chlorokynurenic acid	Transport-plus-conversion is a useful two-step design [65]
Ketoprofen model compound	L-tyrosine-linked prodrug	LAT1-mediated uptake	Demonstrates direct use of a large-neutral-amino-acid transporter [56 and related LAT1 work]
L-dopa + entacapone	Codrug	Combined pharmacological and PK design	Multiple functions can be integrated but increase metabolic complexity [86]
BACE-1 inhibitor leads	Macrocycle / property optimization	Reduce CNS permeability liabilities	Shows that core medicinal chemistry remains important even without a classic prodrug architecture [80]

7. Activation Mechanisms and Release Chemistry

Table 3. Activation mechanisms and release chemistry.

Activation class	Typical chemical handle	Advantages	Limitations / controls
Esterase hydrolysis	Ester / carbonate	Simple synthesis; broad applicability	Often faster in plasma than brain; systemic activation risk

Activation class	Typical chemical handle	Advantages	Limitations / controls
Phosphatase cleavage	Phosphate / phosphonate masking	Powerful polarity switch	Can suffer from broad peripheral phosphatase activity
Redox activation	Dihydropyridine / redox pair	Potential brain trapping	Complex kinetics and oxidation-state control
Disulfide reduction	Disulfide linker	Intracellular trigger	Reducing environment varies by compartment
Oxidative activation	Oxidation-sensitive trigger	Can exploit tissue redox biology	Oxidative stress may be disease-dependent
Self-immolative cascade	Trigger + linker	Amplifies a first enzymatic event	Metabolite profiling is essential
Transporter-linked cleavage	Amino-acid / sugar conjugate	Combines entry and release	Transporter selectivity and peripheral expression
Spontaneous cyclization	Latent nucleophile / electrophile	Can accelerate release after first trigger	Chemical stability must be carefully tuned

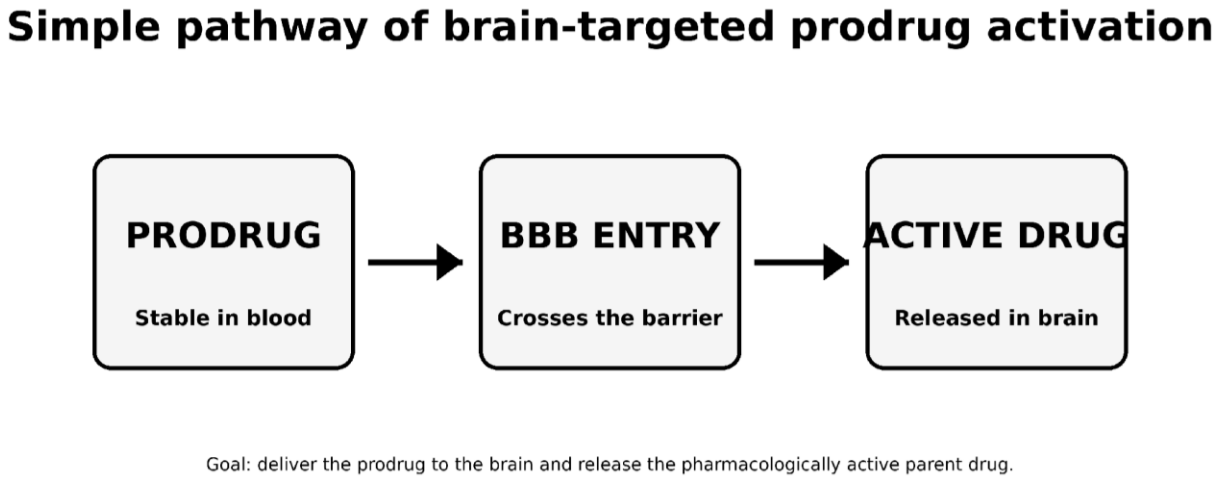

Figure 3. Simple pathway of brain-targeted prodrug activation: systemic stability, BBB entry, and release of the active drug in the brain.

8. Efflux Transporters and Net Brain Exposure

A prodrug can exhibit good permeability in a static assay yet fail in vivo because directional efflux lowers net brain delivery. P-glycoprotein, BCRP and other ABC transporters therefore need to be considered as part of the structure–activity relationship rather than as a late-stage pharmacokinetic nuisance [70–80]. A useful experimental concept is the efflux ratio in a polarized in vitro system; however, in vivo transporter abundance, regional expression, plasma protein binding and metabolism can all change the relationship between in vitro and in vivo behavior.

One medicinal-chemistry option is to lower the affinity of the prodrug for efflux transporters while preserving the desired influx interaction. Another is to design the prodrug so that it is converted after entering the endothelial cell or brain extracellular space. If the released parent drug is too polar for back-diffusion, this can create a pharmacological "lock-in" effect. The design should be evaluated with bidirectional transport and active metabolite measurements rather than with one apparent-permeability value.

9. Disease-State and Regional Considerations

BBB permeability and transporter expression change with neuroinflammation, ischemia, tumors, neurodegeneration and aging. A disease-associated change can either improve access to a prodrug or create a new source of peripheral or endothelial metabolism. Therefore, prodrug programs aimed at pathological tissue should include disease-relevant models and, when possible, human biomarkers of the activating enzyme or transporter [3, 4, 70–80].

Tumor tissue adds another complexity: the blood–brain tumor barrier can be more heterogeneous and permeable than the normal BBB, but this does not mean that diffuse distribution throughout infiltrative

tumor regions is guaranteed. For CNS oncology, a prodrug may need both vascular delivery and tumor-cell activation, making transporter and enzyme heterogeneity central design considerations.

10. Preclinical Evaluation Strategy

Table 4. Preclinical evaluation strategy.

Stage	Key experiments	Decision metric	Common failure mode
1. Computational triage	cLogP/logD, pKa, PSA, MW, BBB prediction	Feasible chemical property space	Over-reliance on a single BBB model
2. Chemical stability	Buffer, plasma, liver, microsomes	Half-life / % remaining	Premature hydrolysis
3. Transport	PAMPA, BBB endothelial models, bidirectional assays	Papp and efflux ratio	False-positive permeability
4. Bioactivation	Brain and plasma homogenates; enzyme panels	Parent formation rate	Weak or nonspecific activation
5. In vivo PK	Plasma + brain + major tissues	Brain/plasma ratio; parent/prodrug AUC	High prodrug but low parent exposure
6. PD / target engagement	Biomarker or functional endpoint	Exposure–response relationship	Brain concentration without pharmacology
7. Safety / translation	Metabolites, off-targets, species comparison	Therapeutic index	Species-specific metabolism

11. BBB Models for Prodrug Evaluation

Table 5. BBB models for prodrug evaluation.

Model	Best use	Strength	Limitation
PAMPA-BBB	Early permeability screen	Fast and inexpensive	Does not reproduce transporters or metabolism
Primary endothelial cells	Transport and barrier studies	Biological relevance	Variable phenotype and limited scalability
Human iPSC-derived BBB models	Human-relevant permeability	Potentially high barrier fidelity	Standardization and maturation remain challenging
Co-culture with pericytes/astrocytes	Barrier biology	Better neurovascular representation	More complex and lower throughput
Microfluidic BBB-on-chip	Flow and mechanistic transport	Dynamic environment	Instrumentation and validation burden
Rodent in situ perfusion	Quantitative BBB influx	Mechanistic transport kinetics	Species differences
In vivo PK/brain homogenate	Actual exposure	Integrates physiology	Does not localize cellular distribution by itself
Imaging / microdialysis	Spatial or free-drug information	Closer to target-site exposure	Technically demanding

12. Computational and AI-Assisted Design

BBB prediction has shifted from simple empirical rules to machine-learning and graph-based models capable of encoding molecular framework and drug-protein relationships. Such methods can rank chemical series but do not remove the need for experimental confirmation since transporter dependence, plasma binding, active metabolism and assay-specific labels can confound predictions [55 and contemporary literature]. The most informative computational workflow is multi-objective: optimize permeability, low efflux, synthetic

feasibility, stability, activation selectivity and safety together, rather than maximizing a single BBB score.

Generative models can also sample chemical space by proposing structures that jointly satisfy target affinity and predicted CNS properties. Train sets that distinguish between passive BBB permeability and measured brain exposure, and differentiate parent-drug vs. prodrug concentrations, will likely increase their value. A model trained only on binary BBB labels cannot learn whether a prodrug succeeds by activation or by passive diffusion.

13. Translational Decision Matrix

Table 6. Translational decision matrix.

Scenario	Preferred strategy	Why	Critical monitoring
Highly polar parent; known CNS transporter	Carrier-mediated prodrug	Can bypass passive permeability limits	Transporter specificity; peripheral substrate effects
Parent contains maskable acid/base	Polar-group masking	Simple and modular medicinal chemistry	Plasma stability; brain activation
Need prolonged brain residence	Redox / intracellular trapping	Can create CNS retention	Reaction kinetics; metabolite safety
Target enzyme enriched in brain or disease tissue	Selective enzyme trigger	Potential tissue selectivity	Human enzyme distribution/activity
High P-gp liability	Structure optimization or uptake-targeted prodrug	Improves net brain exposure	Bidirectional transport; in vivo efflux
Combination pharmacology desired	Codrug / multifunctional prodrug	One molecule may combine functions	PK and metabolite complexity

14. Literature Evidence Mapping

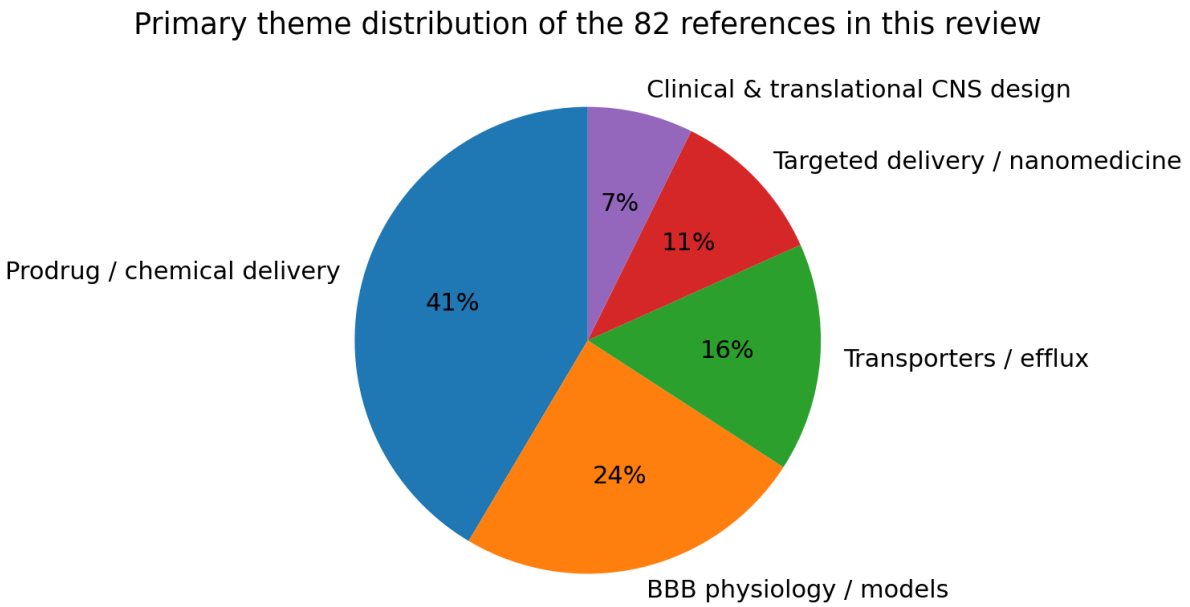

Figure 4. Distribution of the main theme of the 82 references used in this review. For the purpose of visualization, each reference is assigned a single primary theme. For this pie chart, the categories are mutually exclusive and are meant to communicate the composition of the evidence base, not the prevalence of strategies in the field at large.

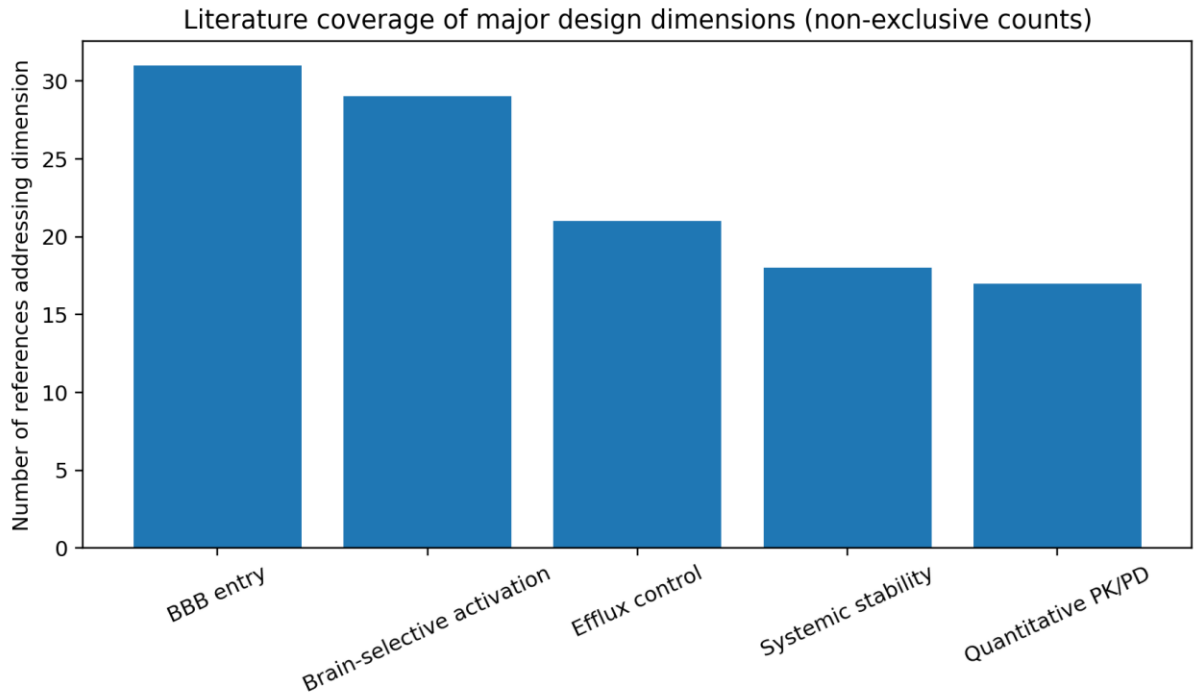

Figure 5. Non-exclusive reference counts for major design dimensions. A single paper may address multiple dimensions, so these bars describe coverage in the selected literature set rather than effect sizes or success rates.

15. Advantages, Limitations and Research Gaps

Table 7. Advantages, limitations and research gaps.

Dimension	Current opportunity	Persistent limitation	Priority research gap
Chemical space	Rapidly tune polarity and ionization	Promoieties may introduce new liabilities	Standardized structure–activation datasets
Transporter targeting	Can deliver polar substrates	Transporter expression is tissue/species dependent	Human BBB transporter phenotype mapping
Activation selectivity	Potential to enrich active drug in brain	Brain-specific enzymes are not always unique	Quantitative tissue enzyme activity measurements
Efflux control	Can greatly alter net CNS exposure	Prediction remains difficult	Integrated uptake-efflux models
Modeling	AI can rank large libraries	Training labels are heterogeneous	Benchmark datasets with measured brain exposure
Translation	Human BBB models are improving	Clinical CNS exposure remains hard to measure	Linked PK–PD–imaging endpoints

16. FUTURE PERSPECTIVES:

The next generation of brain-targeted prodrugs will likely be multifunctional in a single architecture, incorporating a transport-enabling motif, a chemically or enzymatically selective trigger, and a retention mechanism. Rather than simply asking whether a compound crosses the BBB, medicinal chemists will increasingly ask where, by which mechanism, and in what molecular form the compound reaches the brain [81,82].

Three developments are especially important to note. First, human-relevant BBB models and quantitative transporter data should be integrated earlier in medicinal-chemistry campaigns. Second, parent-drug and prodrug concentrations need to be measured separately in plasma and brain so that apparent "brain delivery" is not conflated with prodrug accumulation. Third, computer models should predict mechanism, not just a binary label. These modifications can help shift the focus of brain targeting from empirical optimization to mechanism-based design.

17. CONCLUSION:

The design of brain-targeted prodrugs is a mature, but still evolving, strategy in medicinal chemistry. Reversible structural changes have been historically shown to modulate CNS distribution in chemical delivery systems and transporter-based approaches have shown that endogenous nutrient pathways can be hijacked for therapeutic delivery . The current work is more focused on activation chemistry, tissue selectivity, efflux control and quantitative PK/PD. The main lesson is that only passage of BBB is not enough. To be effective, a candidate must arrive in the brain in a productive form, be activated at the right place and time, reach the right cellular compartment and have an acceptable therapeutic index. This therefore suggests that the most promising design paradigm is a coordinated optimization of molecular transport, activation and pharmacology rather than a single parameter focus on lipophilicity.

List of Symbols and Abbreviations

Abbreviation	Full form
BBB	Blood–brain barrier
CNS	Central nervous system
LAT1	L-type amino acid transporter 1
GLUT1	Glucose transporter 1
ABCB1 / P-gp	ATP-binding cassette subfamily B member 1 (P-glycoprotein)
BCRP / ABCG2	Breast cancer resistance protein
CDS	Chemical delivery system
PK/PD	Pharmacokinetics / pharmacodynamics
PSA	Polar surface area
MW	Molecular weight
logP / logD	Logarithm of the partition / distribution coefficient
pKa	Acid dissociation constant
PAMPA	Parallel artificial membrane permeability assay
iPSC	Induced pluripotent stem cell
AUC	Area under the curve
AZT	Zidovudine

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