Design and Development of CNS Drugs

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Outline

• Neurological disorders
• The brain and blood brain barrier
• Strategies to get compounds into the brain
Key Concepts

• What is required to develop CNS drugs
• What are some of the methods used to get compounds into the brain
Neurological Disorders Requiring Centrally-active Drugs

Depression
Anxiety disorders
Seizure disorders
Schizophrenia
Bipolar disorder
Parkinson’s disease
Alzheimer’s disease
Stroke
Central Nervous System Drug Discovery

• Approximately 7000 drugs in the Comprehensive Medicinal Chemistry database
• Only 5% treat CNS disorders
• Physiological challenges for drug to get into the brain
• Failure rate of CNS drugs is higher than average
• Time from entry into FIH to approval is longer
Drug Distribution of Centrally-active Therapies

~2% of SM enters the brain

Absorption  Metabolism  Systemic Plasma  Blood Brain Barrier
The Blood Brain Barrier

• 1885- Ehrlich reports that parental injection of dyes distribute to all organs except the brain and spinal cord.
• 1898- Bield and Kraus suggest that there is a barrier around the brain
• 1900- Lewandowsky shows that injection of cholic acids or sodium ferrocyanide had no CNS effects; coined the phrase “blood brain barrier” to explain the effects.
• 1967 – EM studies show the existence of a structural barrier around the brain
The Blood Brain Barrier Function

- Controls the movement of molecules into and out of the CNS
- Allows for control of the composition of the interstitial fluid
- Maintains synaptic functioning and neuronal connectivity
- Protects the CNS from toxins and inflammation
- Breakdown in the BBB is seen in several diseases including Parkinson’s disease, Alzheimer's disease, and HIV-1 associated dementia
- Breakdown in the BBB may be an early indication of cognitive impairment
  - PDGFRβ

Nation, D.A. et al. Nature Medicine, 2019, 270-276
How Do Compounds Get into the Brain?

- **Passive Diffusion**
  - Low molecular weight and high lipophilicity

- **Active transport**
  - Utilizes transport proteins

- **Endocytosis**

Nanomedicine. **2012;7(8):1225-1233**
Passive Diffusion -
How do medicinal chemists optimize molecules to get into the brain
Key Physicochemical Parameters

- **logP**
  - Measure of lipophilicity; partition coefficient between an aqueous and lipophilic phase, usually water and octanol
  - Hansch – 1967- Parabolic relationship between logP and hypnotic activity
  - Optimal logP of approximately 2 for CNS activity
  - Refined to show the optimal value for a variety of CNS active molecules is 2.4
Example of logP and Brain Levels

logP = 0.84

logP = 1.2

logP = 1.84
Other Relevant Physicochemical Parameters

• \( \text{logD} \)
  – pH dependent; better descriptor since most CNS molecules have basic groups
  – \( \text{logD} \) should be between 0 and 3

• **Hydrogen Bonding**
  – Increased H bonding capacity is associated with lower permeability
  – Also increases the risk of P-gp recognition
  – **Hydrogen bond donors < 3, Hydrogen bond acceptors < 7, total H-bonds <8**

• **Polar Surface Area**
  – Measure of surface area over all polar atoms
  – Calculated as TPSA
  – **For a CNS compound it should be below 70**

• **Molecular Flexibility and Rotational Bonds**
  – Increased molecular flexibility exerts a negative effect on brain penetration
  – **Rotatable bonds <8**
Physicochemical Parameters

- **pKa**
  - Most CNS compounds contain a charged group
  - pKa around 8.4 is optimal

- **Molecular Weight**
  - Increased MW will lead to decreasing brain penetration
  - MW < 450
Multiparameter Optimization (MPO)

- CNS MPO (Pfizer, 2010)
- LogD and MW are better predictors than logD alone
- Developed scoring functions that combine multiple parameters into a single value
- Use clogP, clogD, MW, TPSA, HBD count, and pKa
- Assign a value of 0-1 for each property with 0 being undesirable and 1 being highly desirable
- 74% of CNS drugs are greater than or equal to 4

Drug Discovery Today 2017, 22, 965-969
J. Med. Chem. 2017, 60, 5943-5954
Top Prescribed CNS Drugs

Xanax
MW = 309
LogP = 3.1
HBA = 4
HBD = 0
PSA = 43
RB = 1
MPO = 5.8

Seroquel
MW = 383
LogP = 2.1
HBA = 5
HBD = 1
PSA = 73
RB = 6

Zoloft
MW = 307
LogP = 4.8
HBA = 1
HBD = 1
PSA = 12
RB = 2

Trileptal
MW = 252
LogP = 1.7
HBA = 4
HBD = 2
PSA = 63
RB = 1
Efflux Transporters

• Several types of efflux receptors are expressed on brain capillary endothelial cells
• High level of ATP-binding cassette (ABC) transporters
  – Most widely studied and characterized are the P-glycoproteins (P-gp)
  – 12 transmembrane protein; 1280 amino acids
• Responsible for pumping molecules out of the brain
• Large number of small molecules are P-gp substrates
• Further limits the accessibility of small molecules to targets in the brain
Assays to Help Predict Brain Levels

**NeuroPK**
- Measure the levels of a drug in the brain and compare it to plasma levels
- Need to examine free vs bound drug
- Ratio of unbound drug in brain to unbound drug in plasma, $K_{p,uu}$
  - If ratio is 1, good passive permeability
  - If ratio is less than 1, substrate for an efflux transporter
  - If ratio is greater than 1 an influx transporter is involved

![Chemical Structures]

Venlafaxine $K_{p,uu} = 0.98$

Atenolol $K_{p,uu} = 0.04$

Oxycodone $K_{p,uu} = 3.1$

Diphenhydramine $K_{p,uu} = 5.5$

J. Med. Chem. 2013, **56**, 2-12
**Assays to Help Predict Brain Levels**

- Microdialysis can be used to see if a compound is in the brain
  - Usually used on only a few compounds within a series
- PET imaging
- P-gp knock out mice to determine efflux
Examples of Designing Compounds That Get into the Brain

**Schizophrenia**

- Chronic mental illness that effects 0.5 – 1.0 % of the population
- Symptoms are classified as positive, negative, or cognitive
  - Positive
  - Negative
  - Cognitive

Bipolar Disorders, 2015 http://bipolarsymptoms.com/schizophrenia-symptoms/
Examples of Designing Compounds That Get into the Brain

*Schizophrenia*

- Majority of drugs focus on dopaminergic receptors such as D2 and serotonin receptor 5-HT2a.

- Approaches have emerged that involve non-dopaminergic receptors

Research Directions in Schizophrenia Treatment: Mechanisms of Action for Next-Generation Agents
https://www.medscape.org
First generation vs second generation antipsychotics

- First generation (typical) medications
  - Focused on dopamine antagonism
  - Effective against the positive effects of schizophrenia
  - Due to involvement of dopamine in movement may have motor side effects
- Second generation (atypical) medications
  - Focus on non-dopaminergic pathways
  - Have effects on negative symptoms
  - Side effect profile is more favorable
Phosphodiesterase 10 Inhibitors

- PDE10A highly expressed in the medium neuron of the striatum which is the region most associated with schizophrenia
- PDE10 inhibitors may be useful treating all three major symptoms of schizophrenia
- Targets cAMP and cGMP and not dopamine
- Potentially devoid of some of the side effects associated with agents directly acting on dopaminergic receptors
PDE10 Inhibitors - Reducing HBD

HBD = 3
Poor brain exposure

HBD = 2

HBD = 1
Increase brain levels

J. Med. Chem. 2013, 56, 8781-8792
PDE10 Inhibitors - Reducing PSA and Efflux out of brain

TPSA = 91
ER = 6.2

TPSA = 82
ER = 2.0

TPSA = 65
ER = 0.56

α7 Nicotinic Acetylcholine Receptor Agonists

• Neuronal nicotinic acetylcholine receptors- ligand gated ion channels.
• α7 Nicotinic acetylcholine receptor is one of the most abundant subtypes found in the brain.
• Highly expressed in the cerebral cortex and hippocampus.
• Reduced expression of the receptor in brain tissue from schizophrenia patients
• May help with cognitive and negative symptoms of schizophrenia
α7 Nicotinic Acetylcholine Receptor Agonists – Modulation of pKa

CHRFAM7A gene expression in schizophrenia: clinical correlates and the effect of antipsychotic treatment
BMCL, 2013, 23, 1684 – 1688
Prodrugs
Prodrugs

• Bioreversible derivatives of drug molecules that undergo a chemical or enzymatic biotransformation to the active forms within the body
• Overcomes pharmacokinetic limitations of parent drug
• Chemically modify a drug to become more lipophilic
• Specific type used in CNS research is a chemical delivery system (CDS)
• Increase lipophilicity and locks compound into brain preventing it from coming back out via efflux mechanism
Prodrugs – Example of a CDS

• Delivery of acetylcholinesterase inhibitor
  – Current drugs are used for the symptomatic treatment of cognitive effects in Alzheimer’s disease
  – Eliminate peripheral cholinergic activity

• Delivery of a brain imaging agent

Prodrugs – Example of Using a Brain Enzyme for Activation

- Prodrug for delivery of thyromimetic sobetirome
- Utilize fatty acid amide hydrolase (FAAH)
- May be beneficial in MS
- Eliminate peripheral thyroid activity

50-fold increase in brain levels

ACS Chem. Neurosci. 2017, 8, 2468-2476
Active Transport-
How do medicinal chemists optimize molecules to get into the brain
Example of a Drug Using the Transporter LAT1

- Parkinson’s disease is characterized by a low level of dopamine
- Dopamine will not cross the blood brain barrier
- 1967 L-Dopa is approved
- Arvid Carlson Nobel prize 2000; William Knowles Nobel Prize 2001
Example of Conjugating a Drug to a LAT1 Substrate

J. Contr. Rel., 2017, 261, 93-104
Mol. Pharmaceutics, 2011, 8, 1857-1866
Example of Conjugating a Drug to Glucose and Vitamin C transporters

- Utilize transporters for glucose and transporter for vitamin C
- Release ibuprofen in the brain
- Dual targeting prodrug showed neuroprotective effect compared with control

Drug Delivery, 2018, 25, 426-434
Receptor Mediated Transport

- Certain large molecule peptides in the blood undergo receptor mediated transport across the BBB via endogenous peptide receptors
- Insulin uses the BBB insulin receptor
- Transferrin is transported across the BB using the endogenous transferrin receptor
- Molecular Trojan Horse technology (MTH) utilizes these and related systems to transport molecules into the brain
Receptor Mediated Transport

• Parkinson’s Disease
  – Glial-derived neurotrophic factor (GDNF) is a protein that promotes the survival of dopaminergic neurons
  – Does not get into the brain
  – Fusion protein of GDNF coupled with the transferrin recognition antibody
  – Significant improvement in three models of PD

• Epilepsy, Pain
  – Metabotropic glutamate receptor-1
  – Antibody antagonist of mGluR1 coupled to a single-domain antibody
  – 20-fold increase in brain levels

The FASEB Journal 2017, 30, 1927-1940
Clinical Pharm. and Therap. 2015, 97, 347-361
Other mechanisms to get compounds into the brain
Alternative Approaches

• Cyclodextrins
  – Consist of cyclic oligosaccharides
  – Modify efflux of drugs
  – Tight junctions
• P-glycoprotein inhibitors
• Nose to brain delivery
• Disruption of the blood brain barrier

Kung, Y. et al. Scientific Reports, 2018, 2218
Nanotechnology

- Nanomedicine 2017, 12, 237-253
  - Iron coated liposomes containing nimodipine
  - Efficacious in animal models of Parkinson’s Disease

  - PLCL (polymer) nanoparticles containing lamotrigine
  - Used to treat epilepsy and bipolar disorder
  - Observe high levels in the brain
  - Can tune by altering the composition of the polymer

Pellosi, D. Mol. Pharmaceutics, 2019
Using the BBB to prevent a molecule from exerting its effect

• Receptors for certain drugs may not be restricted to the brain
• What do you do if you want to keep a molecule out of the brain?
• Rimonabant – selective CB1 Antagonist for weight loss
• Serious CNS side effects

Repairing the BBB

Epilepsy

• Approximately 50 million cases in the world
• Blood brain barrier leakage may contribute to seizures
• Matrix metalloprotease inhibitors may be useful for repairing the BBB

Stroke

• Use curcumin delivered in a nanoparticle to repair leakage

Wang, Y. et al. ACS Appl. Mater. Interfaces, 2019, 3763-3770
Summary

• The blood brain barrier prevents most small molecules from entering the brain
• Chemists have a variety of predictive tools that they employ to design compounds that can get into the brain
• Transporters can be utilized to shuttle drugs into the brain
• New methods involving fusion of antibodies, nose to brain technologies, and nanotechnology will aid in the future delivery of drugs
References


Computational modeling in glioblastoma: from the prediction of blood-brain barrier permeability to the simulation of tumor behavior. Miranda, Ana; Cova, Tania; Sousa, Joao; Vitorino, Carla; Pais, Alberto Future Medicinal Chemistry (2018), 10, 121-131.


Crossing the Blood-Brain Barrier: Recent Advances in Drug Delivery to the Brain. M. Patel, B. Patel CNS Drugs. 2017


Questions
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