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
Schizophrenia
Bipolar disorder
Parkinson’s disease
Seizure disorders
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
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

log P = 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

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 is 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

![Venlafaxine](image1)
$K_{p, uu} = 0.98$

![Atenolol](image2)
$K_{p, uu} = 0.04$

![Oxycodone](image3)
$K_{p, uu} = 3.1$

![Diphenhydramine](image4)
$K_{p, uu} = 5.5$

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
- Majority of drugs focus on dopaminergic receptors such as D2 and serotonin receptor 5-HT2a.
- Approaches have emerged that involve non-dopaminergic receptors
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
GlyT1 Inhibitors

• Hypofunction of glutamatergic system NMDA receptors may play a role in schizophrenia
• Restoring NMDA function may represent a novel means of treating the disease
• Glycine is required for activity of the NMDA receptor
• Increase glycine levels in the brain by inhibiting its uptake by the glycine transporter GlyT1
GlyT1 – Reduce PSA to Improve Brain Penetration

PSA = 80
Low brain levels

PSA = 69
Excellent brain levels - Phase II

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

BMCL, 2013, 23, 1684 - 1688
Prodrugs

Efficient Delivery of RNAi Prodrugs, igtrcn.org
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

- Prodrug for delivery of acetylcholinesterase inhibitor
- Utilize oxidation in the brain
- Current drugs are used for the symptomatic treatment of cognitive effects in Alzheimer’s disease
- Eliminate peripheral cholinergic activity

ACS Chem. Neurosci. 2015, 6, 737-744
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

- Ketoprofen – Neuroinflammation
- Valproic acid – Seizure Disorders

Mol. Pharmaceutics, 2011, 8, 1857-1866
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

Clinical Pharm. and Therap. 2015, 97, 347-361
The FASEB Journal 2017, 30, 1927-1940
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
Nanotechnology

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

• J.Con.Rel. 2017,246, 96-109
  • Nanoparticle containing docetaxel for the treatment of brain metastatic breast cancer
  • Coated the surface of the nanoparticle with polysorbate 80 (LDL mediated transport)
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
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Medicinal Chemical properties of Successful Central Nervous System Drugs. NeuroRx., 2005, 2, 541-553.
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