**MECHANISMS OF DRUG VARIABILITY IN BRAIN DISEASES:**

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**THE BLOOD BRAIN BARRIER**

**BBB:**
- The brain absolutely requires a stable environment → maintained by the capillary network supplying blood to the brain = brain blood barrier (BBB)
- The BBB is both physical and a delicately balanced set of transport mechanisms

**STRUCTURAL ASPECTS OF THE BBB THAT DIFFER FROM PERIPHERAL VASCULATURE:**
- Brain endothelial cells are joined by tight junctions of high electrical resistance providing an effective barrier against paracellular movement of molecules
- In peripheral endothelial cells there is good transcellular movement of molecules – there is no such movement in brain endothelial cells
- Brain capillaries are in contact with ends of the astrocytes which essentially separate the capillaries from the neurons

**OTHER BBB CELLS:**
- Pericytes: contractile cells sit adjacent to endothelial cells
  - Help regulate vascular tone and blood flow
  - Assist with immune fxn (removal of cellular debris)
  - Act as another layer to keep the BBB impermeable
  - Deficiencies in pericytes → cause BBB to breakdown
- Astrocytes: form the astroglial sheath (aka astrocytic sheath) in the brain and spinal cord
  - Support roles for both neurons and endothelial cells by exchanging ions and nutrients
  - Coverage can be up to 90%

**WHY THE BBB CAPILLARIES ARE DIFFERENT:**

**Peripheral capillaries**
- Compounds can diffuse across the endothelium
- Compounds can use the paracellular pathway (intercellular pore)
- Compounds can use fenestrations (breaks in the continuity of the endothelium)
- Compounds can use facilitated diffusion and active transporters for influx AND efflux

**Brain capillaries**
- Fat soluble compounds can diffuse through (via lipid membranes of cells)
- Water soluble molecules (ions) are unable to transverse without use of specialized carrier-mediated transport mechanisms
- Junctions between endothelia are tight, no paracellular pathway and no fenestrations unless diseased
- Very little vesicular transport
- Active transporters exist, but mostly efflux compounds back into the blood

**GENERAL PROPERTIES OF DRUGS THAT EASILY CROSS THE BBB:**
- Very fat soluble
- Very small
- Non-ionized
- Exceptions: lithium (ionized); cocaine (water-soluble)

**WHAT TRANSPORTER PROTEINS ARE IMPORTANT IN THE BBB?**
- Transporter proteins play an important role in the BBB
- Substrate specificity, expression levels, and activity of uptake and efflux transporters that are expressed in the BBB differ widely from other tissues in body
- Primarily, the BBB expressed efflux transporters on the Apical membrane, that reflux (efflux) substrates back into the blood = protective mechanism
  - The two most important efflux transporters on the apical membrane are MDR1 (also called P-gp) and BCRP = members of the ABC family of transport proteins (others expressed in humans include MRP1, MRP4, MRP5)

**SO CAN WE USE TRANSPORTERS TO DRIVE DRUGS INTO THE BBB?**
- This is a very current topic of investigation ...
- On the apical membrane (in humans):
  - OATP 2B1 and OATP 1A2 are expressed = organic anion transport protein family
  - Monocarboxylate importer (MCT1), primarily involved in bringing in acids for cellular homeostasis
- On both the apical and basolateral membrane is the transporter LAT1 (human L-type amino acid transporter)
  - Primarily used for importing biochemicals required for cellular (and brain) death
- On the basolateral membrane alone there is evidence for OCTN2 (organic cation transporter (type 2))
CURRENT ISSUES IN PK WITH NEURO DRUGS MEDIATED BY TRANSPORTERS:

**Epilepsy drugs**
- Some people have higher expression of P-gp = resistant to anti-epileptic drugs by preventing them from entering the brain = need higher doses of drugs (compared to others with the same severity of disease)
- Drugs affected include: carbamazepine, felbamate, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate

**Anti-HIV drugs**
- Resistance to HIV viral load suppression and higher levels of neuro-AIDs in people with greater:
  - P-gp: amprenavir, idanavir, nelfinavir, ritonavir, saquinavir
- BCRP: lamivudine

**Anti-cancer drugs**
- Brain tumors are some of the most lethal cancers, primarily because they respond poorly (lack of response) to current therapies
  - Chemotherapy has assumed an important role in their treatment, but systematically administered chemotherapeutic drugs show poor efficacy in the treatment of malignant primary or metastatic brain tumors
- Drugs affected for P-gp include: doxorubicin, daunorubicin, docetaxel, etoposide, idarubicin, methotrexate, mitoxantrone, paclitaxel, teniposide, vinblastine, vincristine
- Drugs affected for BCRP include: anthracyclines (ex// doxorubicin), bisantrene, irinotecan, methotrexate, mitoxantrone, topotecan
- All of the above are also affected by the expression of MRP1,2,3,4,5 (and maybe 6)

**Antipsychotics & antidepressants**
- Extremely variable response to these drugs are hallmarks of the classes
- It is now understood that some of the variability is due to transporter expression at the BBB and less entry into the brain

ANTIPSYCHOTICS AS AN ILLUSTRATIVE EXAMPLE OF OTHER NEURO-PK CONSIDERATIONS:
- Antipsychotic drugs are generally classified according to their mechanism of action and side effect profiles
  - 1st generation (conventional or typical) antipsychotics = high-affinity dopamine D2 receptor antagonism
  - 2nd generation (atypical antipsychotics) = high affinity D2 and S-HT2A antagonists activity
- In general, the antipsychotic drugs (and most drugs for brain disorders) are small, lipophilic and enter the brain well by diffusion

ANTIPSYCHOTICS AND PK DIFFERENCES WITH SEX
- Women experience more AEs more frequently than men for antipsychotics
  - Previously unknown if this was PK or PD in nature
- Sex-related differences of PK have been shown in the PK of CYP450 (higher activity in females for CYP3A4/2D6)
  - However, significantly higher plasma concentrations in women have been demonstrated only for olanzapine and clozapine (so this doesn’t explain everything)
- There are various examples of drugs that differ with generalized sex characteristics such as bodyweight, organ size, or body composition
  - Female-specific PK differences include: absorption, protein binding, Vd, metabolism of drugs due to hormonal influences
  - Women have lower gastric acid secretion, lower GI blood flow and a longer gastric emptying time
  - Women have larger lipid compartments → prolonged half-lives → probable accumulation of lipophilic anti-psychotics
    - This suggests need for longer dosing intervals in pregnancy
    - HOWEVER, amniotic fluid = water compartment that is also distributive, so this argument is difficult to support
- Evidence for female sex differences
  - Higher clozapine and olanzapine plasma concentrations
  - Higher prolactin levels
  - Higher prevalence of osteoporosis
  - Larger increase in bodyweight
  - Higher prevalence of metabolic syndrome
  - Greater QTc interval prolongation & higher incidence of TdP

LONG-ACTING FORMULATIONS
- In affective disorders, longer-acting formulations may be desirable:
  - Increases compliance
  - Decreases peaks & troughs – long-acting formulation (slow release) looks more like an infusion
  - Can have longer intervals between administration, decreases patient discomfort and disruption
- Issues include:
  - Primarily come as IM depot injections but not all injection sites are created equal (most are in gluteus or deltoid)
  - Sudden changes that alters blood flow can affect absorption & distribution = changes therapeutic levels
  - Formulations are very important (crystalline vs. emulsion can have different systemic drug profiles)
  - If there is a sudden drop in drug blood levels (formulation released too fast; drug sequestered due to differential partitioning such as accumulation in fatty compartments in the obese, or systemic drug profile causing increased blood flow to the depot site)
    - Patient can experience break-through sx (i.e. their disorders are not controlled)
    - Can result in increasing resistance to medication management
- The problem with SES and ADRs:
  - If the patient experiences an ADR, the drug cannot be withdrawn quickly due to the depot nature of drug
    - ex// migraine headaches caused by depo-provera
  - (MORE RARELY) If Ka is too high from the depot, patient can experience sudden overdose toxicity that may be prolonged because of the depot nature of the drug

ALTERNATIVE STRATEGIES FOR DIRECT-ENTRY:
- The primary routes of administration for targeting the brain are oral and injectable (IM for long-term, IV for acute)
- Commercially available products with alternative routes include:
  - Loxapine for inhalation
  - Asenapine for SL administration
  - Selegiline for transdermal administration
- Case reports and studies describe:
  - Intranasal, sublingual, and transdermal routes of administration of antipsychotic medications
  - Buccal, sublingual, transdermal, and rectal administration of antidepressant medications
- The specific physiochemical properties possessed by most antipsychotic and antidepressant agents tends towards the same physiochemistry generally required for non-traditional (non-oral, non-IV) routes of administration
- The critical PK parameter for exploration of non-traditional routes of administration, in addition to considering pt factors, is drug absorption (and/or formulation)
DRUGS THAT DON'T NORMALLY GET INTO THE BRAIN – BUT HAVE TO: MENINGITIS AS A CASE STUDY

- Bacterial meningitis is a medical emergency; therapy must be begun without delay
  - The mortality rate of untreated disease approaches 100%, and even with good, timely therapy there is high failure (mortality) rate
  - The preferred approach is antimicrobial therapy, along with dexamethasone → clear issue of how to penetrate the brain to kill the bacteria
- There are 3 general requirements of therapy for bacterial meningitis:
  - Use of bactericidal drugs effective against the infecting organism (requires lumbar puncture and identification of the organism)
  - The CSF is a site of impaired immunity (antibodies cannot get into the brain either) = bacteriostatic agents are NO GOOD
  - Use of drugs that enter the CSF, since the BBB prevents macromolecule entry into the CSF
  - Optimizing the efficacy based on the PD characteristics of the antimicrobial drug
- Antimicrobial penetration into CSF is fairly poor when the BBB is normal, so most beta-lactam antibiotics may be considered
  - HOWEVER, in the presence of meningitis there is increased penetration of antibiotics due to: separation of tight junctions, increased number of pinocytotic vesicles
- IV route is preferred, but for patients where repeat cultures are positive despite therapy with parenteral antibiotics, administration of intrathecal (or intraventricular) antibiotics may be considered
  - Intrathecal & intraventricular administration can lead to very quick CSF sterilization in patients with brain infections (not just meningitis)
  - Relapse rate of meningitis and/or ventriculitis is also very low among patients treated this way
  - Intrathecal administration involves direct injection into the spinal canal, or into the subarachnoid space, to distribute into the CSF
  - The drug avoids the BBB by taking advantage of the leaky subarachnoid space
  - Drugs given intrathecally commonly require preparation in hospital or specialized compounding requirements, with specific requirements:
    - Carefully balanced tonicity for optimal dissolution in CSF with no precipitation, pH changes or changes to the toxicity of the CSF
    - No preservatives included in the injection, as preservatives (and other common IV inactive ingredients) can be toxic to the brain
    - Separation of tight junctions
    - Increased number of pinocytotic vesicles

PK/PD INTERACTIONS:

- Increasingly in therapeutics affecting the brain, it is understood that the Ka and/or Kd of the drug for its target may not be the primary effector of drug efficacy and selectivity
  - RATHER, there is a concept of "residence time" = how long a ligand is bound to its target receptor
  - Seen as a means of improving clinical efficacy by increasing target coverage
- Under this concept, it has been proposed that in vivo, the duration of efficacy of receptor-ligand association (i.e. association rate constant aka on-rate (Ka)) and the rate of dissociation (i.e. dissociation rate constant aka off-rate (Kd)) is a binary complex
  - Koff is translated into a dissociative half-life for the receptor-ligand complex = residence time
  - Pharmacokinetically speaking, the residence time is a function of BOTH concentration AND affinity for the receptor
- It has been suggested that differences in the Koff of a drug from its primary target and other cellular secondary targets can provide an informative measure of drug selectivity as it related to the extent of potential adverse effects in vivo
  - What this means is that as drug concentrations in the brain rise, binding to off-target receptors that have lower affinity than the selective receptor, is increasingly likely to happen = analogous to competitive inhibition being a function of concentration
  - THEREFORE, residence time, as an indicator of efficacy, is a combined PK/PD interaction
  - This may also explain why some long-acting formulations show less side effects than same dosages given orally (lack of peak and trough means less chance to bind non-selective receptor, and for less time)
  - The logical place this argument falls down is when the concentration from long acting formulations is maintained the higher therapeutic ranges – then it is dependent for the drug in question
- VISUAL EXAMPLE:
  - If a drug has a Koff for D2 receptor of 20 ng/mL and a Koff for the serotonin receptor of 30 ng/mL, but the therapeutic range spans 10 -50 ng/mL, then even within the therapeutic range you would expect some off-target effects as concentration rises
  - Despite this, the drug will be bound to the D2 target for LONGER because it has a lower Koff (binds tighter)