

08 - Blood brain barrier

Blood-brain barrier

© SPMM Course (Chadwick et al., 2005). Protein binding interactions become relevant in a renal disease where proteinuria can occur. The principle plasma protein responsible for binding to acidic drugs is albumin while α 1-acid glycoprotein is the primary binding protein for alkaline drugs. Most psychotropic drugs are basic, and they may bind to, for example, alpha-1 acid glycoprotein and lipoproteins. Protein binding is 95-99% for drugs like diazepam, chlorpromazine, amitriptyline and imipramine. Protein binding is 90-95% for phenytoin, valproate, and clomipramine. Volume of distribution: $V_d = Q/C_p$, where V_d -volume of distribution, Q -quantity of drug and C_p -plasma concentration at the time of administration ('zero time'). V_d refers to an apparent (not true) volume in which an ingested drug is distributed in the body. The higher the V_d , the lower the plasma concentration. V_d tells us about the characteristics of a drug. When V_d is high, this indicates that the drug has a high affinity for tissues outside body water such as brain and fat. The V_d gives some idea of the whereabouts of the drug in the body. A low value (say 10 or 20 litres) suggests that the drug is concentrated in the blood itself. A high value (say 500 or 1000 litres) indicates that the drug is concentrated in the cells or fatty tissues and not the blood. Increased lipid solubility is associated with increased volume of distribution. This is the case for most psychotropic drugs at physiological pH. If a drug is highly protein bound, its plasma concentration will be high (as proteins exist in plasma), resulting in lower V_d . In other words, V_d is restricted by the total plasma volume for highly protein bound drugs. Tissue binding (e.g. fat or muscle) and accumulation of drugs results in low plasma concentration and, as a result, a high V_d . Hence, competition for protein binding can alter V_d . Blood-brain barrier The distribution of a drug to the brain is governed by 3 factors

1. Brain's regional blood flow
2. Blood-brain barrier
3. Drug's affinity for receptors in the brain Blood-brain barrier is a structural and functional barrier comprised of the capillary endothelium of the brain, which possesses tight junctions, acting in unison as a single sheet or membrane.

© SPMM Course This barrier prevents proteins and other molecules such as immunoglobulins from entering or leaving the brain's blood supply. It also protects the brain from the entry of bacteria, viruses and maintains an osmotic gradient and maintains the cerebral glucose compartment differently from the periphery. Factors that could affect the permeability of the BBB include fever, head injury, hypoxia, hypercapnia, retroviruses, inflammation, vasculitis, hypertension, cerebral irradiation, and aging. The integrity of the BBB can be measured in different ways e.g. by measuring leakiness to labeled IgG molecules or gadolinium. The ability of a drug to pass blood brain barrier depends on its molecular size, lipid solubility and ionic status. Unionized molecules that are freely available and less protein bound are transported across the barrier easily. In general

higher the lipid-water partition coefficient, greater the ability to cross the barrier. Exceptionally there are few molecules that pass the barrier effectively in spite of having a low lipid-water partition coefficient. These have specific carrier mechanisms e.g. aminoacid transport system (this is stereospecific; so l- amino acids not d- amino acids are easily transferred). L-dopa, l-tryptophan and valproate have specific carrier mechanisms. Some small molecules diffuse readily into the brain and CSF from cerebral circulation e.g. lithium ion. Some areas of the brain around the ventricles (circumventricular organs) lack BBB; e.g. subfornical organ, area postrema of the medulla and the median eminence. These circumventricular organs allow the transfer of many compounds from blood to brain. This may have a survival benefit as certain toxic substances stimulate area postrema and induce nausea and vomiting. There is no evidence that inhaled medications bypass the BBB. But to some extent, nasal sprays can reach the brain via olfactory epithelium and bypass the barrier. Anaesthetic agents do not increase the permeability of the blood-brain barrier. In addition to BBB, a blood- cerebrospinal fluid barrier also exists. This is seen in the choroid plexus. Here the tight junctions are located between adjacent epithelial cells, as opposed to adjacent endothelial cells in the case of BBB.

Revision #1

Created 2026-01-04 20:04:14 UTC by Omar Ayman

Updated 2026-01-04 20:04:14 UTC by Omar Ayman