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Neuro pharmacokinetics: the secret life of - old and novel - psychopharmacological drugs

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In the 21st century, the pace of development of new pharmacological treatments for general medical and psychiatric disorders is remarkably different. While successes for the former are frequent, new drugs for mental, behavioral and neurodevelopmental disorders are sporadic. Many factors contribute to this discrepancy. Probably the most important is the complexity of etiology and manifestations of mood, psychotic, anxiety, neurocognitive and other disorders that are commonly treated with psycho pharmacological drugs. Although this factor cannot be directly addressed in drug development, optimization of drug exposure in brain tissue can certainly help to balance the efficacy and safety of both widely used and novel psycho pharmacological drugs. While drug exposure of various organs and tissues can be easily assessed from free (unbound) blood concentrations, the central nervous system (CNS) has a number of barriers, most notably the blood-brain barrier (BBB) that separates nervous tissue from the periphery. Optimised CNS exposure of a drug to its target site over a desired time period is critical to triggering its therapeutic effect. The presence of the BBB readily leads to an asymmetry of drug (unbound) exposure in the brain and in the systemic circulation, which prohibits the use of unbound drug concentration in plasma as a surrogate for unbound drug concentration in the brain. Comprehensive pharmacokinetic/pharmacodynamic studies of marketed CNS drugs have shown that the concentration of unbound drug in brain interstitial fluid is an appropriate measure of CNS exposure in the context of cell membrane targets of action. The more recent concept of brain-plasma partition coefficient, $K_{p,uu}$, as a parameter describing the relationship between the concentration of unbound drug in brain interstitial fluid and the concentration of unbound drug in plasma, is assumed to be the most important means of assessing brain exposure. Experimental assessment of $K_{p,uu}$ requires either measurement of the brain unbound drug concentration in the interstitial fluid by microdialysis *in vivo* or estimation of the fraction of unbound drug in the whole brain homogenate ($f_{u,brain}$) by equilibrium dialysis *in vitro*. $K_{p,uu}$ can be calculated by dividing either the area under the curve (AUC) of the profile of the concentration of unbound drug in brain and plasma after a single administration or the steady-state unbound concentrations of drug in brain interstitial fluid and plasma. Although many marketed psychotropic drugs have $K_{p,uu}$ values as low as 0.1-0.2, it is theorized that the most successful small molecule CNS drugs should have $K_{p,uu}$ values near 1. The neuropharmacokinetic behavior of benzodiazepine compounds, both widely used and those in preclinical and clinical development, is presented as a showcase. Given the variety of receptor subpopulations at which these drugs act as positive allosteric modulators of $GABA_A$ receptors, the complexity of linking brain exposure data to the corresponding pharmacodynamic effect is explained.