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Commentary

The Plasma Proteins of Rats and Developmental Changes in Drug

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DESCRIPTION

Specialized cellular barriers like the blood-brain barrier, the blood-CSF barrier, and the CSF-brain barrier prevent compounds, including drugs, from entering the brain and Cerebrospinal Fluid (CSF). Although these barrier interfaces undergo a number of physical and functional changes as the brain matures, tight junctional complexes present from the earliest stages of development maintain the same passive permeability to lipid insoluble markers. Cellular mechanisms like influx and efflux transporters, on the other hand, can control the passive entry of lipid-soluble compounds through brain barriers. Other factors can also have an effect on the amount of transfer across these interfaces, in addition to mechanisms that are specific to these barriers.

Many of the plasma proteins that move endogenous substances through the blood also interact with circulating therapeutic agents to form complexes that are too big to easily cross cell membranes, which restricts their distribution in tissues. In addition to the physiochemical properties of the drugs and target proteins and their binding affinity, competition with other substances and the relative concentration of proteins, which is known to fluctuate throughout life, during pregnancy, and in a variety of disease states, determine the extent of protein binding.

The blood-brain barrier is nearly impermeable to the passive transfer of most blood plasma proteins under physiological conditions. It has been demonstrated that plasma proteins traverse the epithelium of the choroid plexus intracellularly in the CSF. Their molecular size and plasma concentration are directly related in adulthood to their concentration in the CSF. Drugs that do not bind to plasma proteins can more easily pass through barrier membranes, like the brain's capillary endothelial cells. On the other hand, it is reasonable to anticipate that highly protein-bound drugs will remain in the bloodstream, leading to a decrease in drug accumulation in the brain and consequently a decrease in the pharmacological activities that occur at their target sites. The free drug hypothesis is a common name for this. Drug transfer across brain barriers is also dependent on vascular characteristics like flow rate, capillary volume, rate of dissociation from proteins, and membrane permeability because protein binding is typically a reversible and highly dynamic process. Drugs that do not strictly bind to plasma proteins, for instance, can easily dissociate and spread across cell membranes. However, there is a correlation between protein binding and brain and CSF exposure to many substances that are not subject to active transport.

The ratio of bound to unbound (free) fractions for some drugs may be affected by changes in the concentration of the proteins to which they bind. In every animal species that has been investigated thus far, it is known that the total concentration of plasma proteins is lower earlier in development. However, despite the fact that total protein concentration and the concentrations of the two major drug-binding proteins: While albumin and 1-acid glycoprotein concentrations rise with age, those of other plasma proteins like 1-fetoprotein, fetuin, and transthyretin typically fall. It has been hypothesized that transthyretin and -fetoprotein both have significant drug binding capabilities. Pregnancy also experiences physiological variation in plasma protein concentrations because of an increase in plasma volume and a decrease in albumin concentration.

Understanding their therapeutically active concentrations requires an understanding of the degree to which drug proteins are bound to them. However, when prescribing medications to pregnant and pediatric populations, potential differences in drug protein binding at various stages of development due to changes in the concentration and composition of circulating plasma proteins are frequently overlooked. Using rat plasma from embryonic (E) day 19 fetuses, postnatal (P) day 4 pups, and pregnant and non-pregnant female adult rats, we investigated *in vitro* plasma protein binding of six drugs (digoxin, paracetamol, olanzapine, ivacaftor, valproate, and lamotrigine) and two water soluble inert markers of barrier permeability (sucrose and glyce Molecular size, lipid solubility, and acidity/basicity are just a few of the physiochemical properties covered by this selection of drugs. Digoxin (cardiac glycoside) and ivacaftor (cystic fibrosis transmembrane conductance potentiator) are examples of peripherally acting medications, while olanzapine (an antipsychotic), paracetamol (analgesic and antipyretic), and the seizure medications valproate and lamotrigine (anti-seizure medications) are examples of central nervous system-acting medications. Liquid chromatography coupled to mass

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spectrometry-measured samples from *in vivo* experiments for two of the drugs (lamotrigine and valproate) confirmed the method's validity. Using previously published data, the measurements of the drugs' protein binding have been linked to their levels *in vivo* in the brain and CSF following systemic administration in the discussion.