PALESTRAS

THE BLOOD-BRAIN BARRIER

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Whether electrolytes, colloids, vital dyes or other complex molecules, the rate of penetration of many plasma solutes into the extravascular fluids of the central nervous system is considerably slower than into the extravascular fluids of most other tissues. This phenomenon is present in the lowest vertebrates and can be observed early in embryonic development. It is still demonstrable several hours after death, long after the brain itself ceases to function. This barrier is associated with the entire cerebral vasculature, and a generalized breakdown *in vivo* can be achieved only by drastic measures, which are invariably fatal. The mechanism, even the anatomy, of this unique solute exchange is still obscure.

Anatomical location of the blood-brain barrier — Walter (1929) proposed three distinct barriers: the blood-cerebrospinal fluid (CSF) barrier, the blood-brain barrier and the cerebrospinal fluid-brain barrier. The last is of little significance, since the ependyma of the ventricles and the pia over the cortex do not inhibit any substance in the cerebrospinal fluid, except protein, from penetrating into the brain. In this respect the brain behaves like an amorphous colloidal mass into which substances diffuse from the subarachnoid space according to their concentration gradients and relative mobilities. The other two barriers are functionally quite similar although some intravenous drugs exert their effects on the brain before they can be detected in the cerebrospinal fluid, and Friedmann and Elkeles (1931) believe that basic dyes more readily penetrate the blood-brain barrier whereas acidic dyes more readily penetrate the blood-CSF barrier. In the choroid plexus vital dyes as well as radioisotopes appear to escape readily from the vascular compartment into the adjacent connective tissue, but further passage into the CSF is impeded by the epithelium. Although the concept that the CSF acts as an intermediary between the plasma and the brain for all metabolic exchange has ben discarded, Bakay (1956) supports the view that inorganic phosphate, and perhaps other inorganic ions, are transported primarily by this route.

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The two most probable sites subserving the pan-vascular blood-brain barrier are the capilary endothelium and/or the perivascular membrana gliae limitans. Electron micrographs demonstrate a uniquely thick and solid arrangement of the endothelial cells in brain capillaries which might make them more "leak proof" than capillaries elsewhere. There is also a pericapillary membrane approximately 0.5μ thick composed primarily of astrocytic end feet applied directly to the capillary wall. The adherents of the endothelial hypothesis base their conclusions largely on observations utilizing vital dyes and have marshalled impressive evidence in favor of this barrier locus. However, with respect to inorganic ion impermeability, little evidence is available to implicate directly either the endothelium or the pericapillary astrocytic membrane. Tschirgi and Taylor (1956) suggested that both structures might perform a role in blood-brain barrier activity: the CNS capillary endothelium, like the kidney glomerules, excluding plasma protein transfer almost completely; the astrocytic membrane, like the kidney tubule, regulating the movement of other solutes between the plasma and the CNS.

A further complexity has been introduced by recent electron micrographs of cerebral cortex which demonstrate "absolutely no large-scale extracellular gaps or spaces" (Schultz, Maynard and Pease, 1957). This almost complete absence of interstitial fluid would require that all substances become intracellular in the process of leaving the vascular compartment.

Physiology of the blood-brain barrier — Penetration of solutes from the plasma into the CNS appears to be a special case of cell permeability and is determined, in part, by concentration gradient, molecular size and mobility, electrical charge, lipoid solubility and metabolic activity of the cells. Water moves freely between plasma and CNS; organic crystalloids, like sugars (except glucose) and urea, penetrate the brain slowly; lipoid soluble substances generally pass into the CNS readily; large molecules, like proteins, penetrate hardly at all; inorganic ions differ in their rates of penetration, but are much slower than in other tissues, and their final steady-state concentration ratios in brain may not equal their concentration ratios in the plasma, indicating a selective transport mechanism in the barrier. Glucose movement from plasma into brain appears to involve a complex transfer reaction which is dependent upon a liver factor and cytidine and uridine.

Alterations in barrier permeability — Only extreme measures will increase blood-brain barrier permeability, such as raising blood osmotic pressure by intravenous 20% or greater NaCl; lowering blood pH below 4.0 or raising it above 10.0; increasing body temperature above 45°C for prolonged periods; high concentrations of bile salts, saponin, bee venom, cobra venom, Diodrast, and other toxins; anaphylactic shock; prolonged seizures induced by insulin, metrazol or electric current; and intense head irradiation with X-rays. Hyaluronidase, histamine, acetylcholine (sub-lethal doses) and carbon dioxide are ineffective.

In addition to the areas of CNS normally more permeable to vital dyes and radioisotopes (pituitary gland, pineal body, area postrema, subfornical organ, supraoptic crest and choroid plexuses), CNS tumors, regions of traumatic damage, regions of inflammatory damage and areas of softening resulting from cerebrovascular disorders are associated with increased barrier permeability.

REFERENCES

All references in this summary will be found in one of the following reviews: BAKAY, L. — The Blood-Brain Barrier. Charles C. Thomas, Springfield, 1956. TSCHIRGI, R. D. — Blood-Brain Barrier, in "The Biology of Mental Health and Disease" (The 27th Annual Conference of the Milbank Memorial Fund). New York, Paul Hoeber, 1932, p. 34-46. SCHULTZ, R. L.; MAYBARD, E. A.; PEASE, D. C. — Eletron microscopy of neurons and neuroglia of cerebral cortex and corpus callosum. Amer. J. Anatomy, 100:369-407, 1957. TSCHIRGI, R. D. — Blood-Brain Barrier, in "Biology of Neuroglia", edited by W. F. Windle, Charles C. Thomas Springfield, 1958.