

ESTIMATES OF BRAIN CAPILLARY PERMEABILITY AND BRAIN EXTRACELLULAR SPACE IN Squalus acanthias BY VENTRICULAR PERFUSION

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The fourth ventricle of the brain of Squalus acanthias can be readily perfused by an artificial cerebrospinal fluid (CSF). By employing such a technique information concerning the movement of material between CSF and brain, brain and blood, and extracellular and intracellular brain compartments can be obtained. This can be seen, in brief, from the following. Any material which moves from the CSF into the brain parenchyma may subsequently: diffuse farther into the tissue by way of extracellular channels; or enter the cells (either by diffusion or some other mechanism); or cross the brain capillary endothelium (again, either by diffusion or some other mechanism) and be swept away by the circulating blood; or do a combination of the preceding three possibilities. In this system materials which cross the brain-blood interface (the so-called blood brain barrier) readily will not accumulate in the brain since they are removed by the circulating blood as rapidly as they enter the brain tissue from the perfusate. Materials of moderate capillary permeability will show some accumulation in tissue adjacent to the perfused surface but essentially none in deep tissue. Substances which have little or no brain capillary permeability will remain in the tissue and be distributed in brain cells and/or brain extracellular fluid. Furthermore, if such substances remain primarily extracellular, one can estimate the extent of this space and the apparent rate of movement of such molecules in the extracellular fluid.

Perfusions of the fourth ventricle of the brain with artificial CSF containing various labeled molecules were performed in anesthetized dogfish. From one to two hours after beginning the perfusion, the animals were sacrificed and the medulla rapidly excised. Several slices of the medulla, 0.5 mm thick, were taken starting from the perfused (ventricular or inner) surface and moving outward. The results for  $^{14}\text{C}$ -antipyrine and  $^3\text{H}$ -OH perfusions showed essentially no tissue accumulation, thus these molecules have high brain, capillary permeability in dogfish. Perfusions with  $^{14}\text{C}$ -urea and with  $^{14}\text{C}$ -5-hydroxyindole acetic acid indicated that these substances do cross the brain capillary endothelium but that their relative rate of penetration is much less than that of water or antipyrine. Sizeable amounts of labeled material (12-30% of the CSF concentration) were found in the inner slices. From perfusions with solutions containing  $^{14}\text{C}$ -sucrose or  $^{14}\text{C}$ -inulin, it could be determined that these compounds have very low capillary permeability. The medulla distributions space for sucrose and inulin were 9-14% (relative to the mean perfusate radioactivity). It is likely that this is a fair estimate of the dogfish brain's perivascular extracellular space. Furthermore, the kinetics of the distribution of these two organic nonelectrolytes was consistent with that of diffusion with the diffusion coefficient for each in brain being similar in magnitude to their respective free diffusion coefficient in water at 12-15°C.