BLLOD-BRAIN BARRIER: A GATEWAY TO NEUROLOGICAL DISEASES

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Blood-Brain Barrier (BBB) originally discovered by Paul Ehrlich in 1885 in Berlin when he found that Trypan blue and other aniline dyes did not stain the brain and spinal cord of rabbits after intravenous administration [1]. Later on his disciple Edwin Goldmann in 1912 further added to this that administration of Evans blue into the ventricular system stained deeply the brain tissue, however, the dye could not be seen into the blood stream. These fundamental discoveries in Berlin, Germany about 100 years ago has given two important concepts of the barrier system, namely the blood-brain barrier (BBB) and brain-blood barrier [1-3]. However, very little is known till today about the functional implication of these barriers in health and disease.

Lina Stern proposed the concept of the "blood-brain barrier" in 1921 [3]. At that time it was believed that astrocytes rather than endothelial cells are the seat of the blood-brain barrier because of the densely packed astrocyte processes that surround the epithelial cells of the BBB [2.3]. However, the role of endothelial cells in maintaining the barrier functions was only established in 1960s when the scanning electron microscope was available [2]. Transmission electron microscopy demonstrated presence of tight junctions between cerebral endothelium that comprise the physical part of the BBB [1,2]. The barrier between blood and cerebrospinal fluid (CSF) was discovered by Hugh Davson in 1959. Electron microscopic studies further show that the endothelial cells of the choroid plexus are fenestrated and do not constitute the barrier. On the other hand, the tight junctions are located between apical sides of the choroid epithelium constituting the anatomical seat of the blood-CSF barrier (BCSFB). However, the BCSFB is less restrictive than the BBB located within the cerebral endothelium. Interestingly, these barriers are compromised in all the known neurological diseases so far. However, treatment strategies are still not directed towards restoration of these barriers within the brain. Thus, the functional significance of these disrupted barriers and neuroprotection is still not well elucidated [1].

Our laboratory initiated experimental models on BBB disruption to see whether breakdown of the BBB leads to brain damage. Using various animal models of emotional stress, (restraint, forced swimming, sleep deprivation, hyperthermia); traumatic insults (incision of peripheral nerves, spinal cord or brain) or chemical insults (serotonin, histamine or prostaglandin infusion); psychostimulants addiction or withdrawal stages (morphine, methamphetamine, MDMA, cocaine) and exposure to nanoparticles (from metals, Ag, Al, Cu, Mn) we observed a selective and very specific disruption of the BBB in several parts of the brain [1,4]. Breakdown of the BBB was associated with altered cognitive and motor functions, slowing of EEG changes, formation of vasogenic edema, and expression of various early genes and induction of brain pathology [1]. Prevention of BBB leakage by drugs, antibodies, neurotrophins or receptors blockers to several neurochemical agents attenuated brain dysfunction and brain pathology. Taken together these observations suggest that BBB may be considered as a "gateway to neurological diseases", a hypothesis still being tested in our laboratory using new morphological and biochemical approaches.

References

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