Blood-brain barrier disruption

Disruption of the blood-brain barrier refers to a condition in which the barrier's integrity is compromised, leading to increased permeability and allowing substances that are normally restricted from entering the brain to pass through. This disruption can be temporary or more sustained, and it can have significant implications for brain health and function.

Several factors can contribute to blood-brain barrier disruption:

Injury and Inflammation: Traumatic brain injury, stroke, infections, and neuroinflammatory conditions can lead to an inflammatory response that can weaken the blood-brain barrier and make it more permeable.

Neurological Disorders: Certain neurological disorders, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease, are associated with blood-brain barrier dysfunction. The breakdown of the barrier might contribute to disease progression and the infiltration of immune cells into the brain.

Medical Procedures: Certain medical procedures, such as radiation therapy for brain tumors or neurosurgery, can cause localized disruption of the blood-brain barrier.

Hypertension: High blood pressure can contribute to blood-brain barrier dysfunction, possibly due to the increased stress on the blood vessels.

Toxic Substances: Exposure to certain toxins, drugs, or chemicals can compromise the integrity of the blood-brain barrier.

Aging: The blood-brain barrier can become more permeable with age, potentially contributing to the increased susceptibility of older individuals to certain brain disorders.

Disruption of the blood-brain barrier can lead to various consequences:

Neuroinflammation: Immune cells and inflammatory molecules may enter the brain, contributing to chronic neuroinflammation, which is implicated in various neurological disorders.

Toxic Buildup: Harmful substances that are normally kept out of the brain can accumulate, potentially causing damage to brain cells.

Altered Brain Function: Changes in the brain's microenvironment due to BBB disruption can affect brain function and behavior.

Medication Delivery: In some cases, BBB disruption can be intentionally induced to facilitate the delivery of drugs to the brain for the treatment of certain conditions, such as brain tumors.

Researchers are actively investigating ways to mitigate blood-brain barrier disruption and develop strategies to repair it when necessary. This area of study is crucial for understanding brain health, neurological disorders, and potential treatments.

Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2 [1)]

Tumor Treating Fields (TTFields), approved for glioblastoma (GBM), affect the BBB's integrity and permeability. Salvador et al. treated murine microvascular cerebellar endothelial cells (cerebEND) with 100-300 kHz TTFields for up to 72 h and analyzed the expression of barrier proteins by immunofluorescence staining and Western blot. In vivo, compounds normally unable to cross the BBB were traced in healthy rat brain following TTFields administration at 100 kHz. The effects were analyzed via MRI and immunohistochemical staining of tight-junction proteins. Furthermore, GBM tumor-bearing rats were treated with paclitaxel (PTX), a chemotherapeutic normally restricted by the BBB combined with TTFields at 100 kHz. The tumor volume was reduced with TTFields plus PTX, relative to either treatment alone. In vitro, they demonstrated that TTFields transiently disrupted BBB function at 100 kHz through a Rho kinase-mediated tight junction claudin-5 phosphorylation pathway. Altogether, if translated into clinical use, TTFields could represent a novel CNS drug delivery strategy [2)].

The blood-brain barrier (BBB) can be easily destroyed by stroke, which is one of the main factors responsible for macrophage infiltration and central nervous inflammation.

The blood-brain barrier represents a fundamental limitation in treating neurological disease because it prevents all neuropeptides from reaching the central nervous system (CNS). Currently, there is no efficient method to permanently bypass the blood-brain barrier.

Activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPAR) is thought to cause acute brain injury, but the role remains poorly understood in subarachnoid hemorrhage (SAH).

A study was conducted to evaluate if AMPAR activation induces acute blood-brain barrier disruption after SAH. C57BL/6 male adult mice (n = 117) underwent sham or filament perforation modeling, followed by a random intraperitoneal injection of vehicle or two dosages (1 mg/kg or 3 mg/kg) of a selective non-competitive AMPAR antagonist perampanel (PER) at 30 min post-modeling. The effects were evaluated by mortality, neurological scores, and brain water content at 24-48 h and video electroencephalogram monitoring, immunostaining, and Western blotting at 24 h post-SAH. PER significantly suppressed post-SAH neurological impairments, brain edema, and BBB disruption. SAH developed epileptiform spikes without obvious convulsion, which were also inhibited by PER. Western blotting showed that the expression of AMPAR subunits GluA1 and GluA2 was unchanged after SAH, but they were significantly activated after SAH. PER prevented post-SAH activation of GluA1/2, associated with the suppression of post-SAH induction of tenascin-C, a causative mediator of post-SAH BBB disruption. Meanwhile, intracerebroventricular injection of a subtype-selective GluA1/2 agonist augmented the activation of GluA1/2 and the induction of tenascin-C in brain capillary endothelial cells and aggravated post-SAH BBB disruption without increases in epileptiform spikes. Neurological impairments and brain edema were not correlated with the occurrence of epileptiform spikes. This study first showed that AMPAR plays an important role in the development of post-SAH BBB disruption and can be a novel therapeutic target against it [3)].

Zang et al. reported the protective effects of Trelagliptin against BBB injury and macrophage infiltration. The results indicate that the infraction volume, the neurological score, and macrophage infiltration staining with CD68 were increased in middle cerebral artery occlusion (MCAO) mice but significantly reversed by treatment with Trelagliptin. Additionally, Trelagliptin reduced the permeability of the BBB by increasing the expression of the tight junction zonula occludens protein-1 (ZO-1) in the cerebral cortex. In an in vitro hypoxia model of endothelial cells, the increased migration of macrophages, enlarged permeability of endothelial monolayer, downregulation of ZO-1, and elevated expression level of CXCL1 by hypoxic conditions were all reversed by treatment with Trelagliptin in a dose-dependent manner. The results demonstrate that Trelagliptin might mitigate macrophage infiltration by preventing the breakdown of the blood-brain barrier in the brains of MCAO mice [4)].

Although ongoing research has yielded some potential options for future glioblastoma therapies, delivery of chemotherapy medications across the BBB remains elusive and has limited the efficacy of these medications [5)].

Current strategies for enhancing the delivery of therapies across the BBB to the tumor is discussed, with a distinction made between strategies that seek to disrupt the BBB and those that aim to circumvent it in the article of Azad et al. [6)].

Histological investigations have shown that disruption of the blood brain barrier (BBB) is well correlated with the degradation of collagen IV, a major component of the BBB [7)]. Among other basal lamina proteins, collagen IV is often degraded by metalloproteinase-9 (MMP-9)

Triolein emulsion infusion into the carotid artery has been reported to induce temporary and reversible opening of the blood brain barrier by increasing vascular permeability.

Transmucosal delivery of glial derived neurotrophic factor (GDNF) is equivalent to direct intrastriatal injection at ameliorating the behavioral and immunohistological features of Parkinson's disease in a murine model. Mucosal grafting of arachnoid defects is a technique commonly used for endoscopic skull base reconstruction and may represent a novel method to permanently bypass the blood-brain barrier [8)].

1)
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