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REVIEW ARTICLE

The Blood–Brain Barrier as a Target in Traumatic Brain Injury Treatment

Serge C. Thal[a] and Winfried Neuhaus[b,c]

[a]Department of Anesthesia and Critical Care, Johannes Gutenberg University, Mainz, Germany
[b]Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse, Vienna, Austria
[c]Department of Anesthesia and Critical Care, University Hospital Wuerzburg, Wuerzburg, Germany

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Traumatic brain injury (TBI) is one of the most frequent causes of death in the young population. Several clinical trials have unsuccessfully focused on direct neuroprotective therapies. Recently immunotherapeutic strategies shifted into focus of translational research in acute CNS diseases. Cross-talk between activated microglia and blood–brain barrier (BBB) could initiate opening of the BBB and subsequent recruitment of systemic immune cells and mediators into the brain. Stabilization of the BBB after TBI could be a promising strategy to limit neuronal inflammation, secondary brain damage and acute neurodegeneration. This review provides an overview on the pathophysiology of TBI and brain edema formation including definitions and classification of TBI, current clinical treatment strategies, as well as current understanding on the underlying cellular processes. A summary of *in vivo* and *in vitro* models to study different aspects of TBI is presented. Three mechanisms proposed for stabilization of the BBB, myosin light chain kinases, glucocorticoid receptors and peroxisome proliferator-activated receptors are reviewed for their influence on barrier-integrity and outcome after TBI. In conclusion, the BBB is recommended as a promising target for the treatment of traumatic brain injury, and it is suggested that a combination of BBB stabilization and neuroprotectants may improve therapeutic success.

Key Words: Blood–brain barrier, Brain injury, Immune cells, Neuronal inflammation.

Introduction

Traumatic brain injury (TBI) is a result of a direct or indirect mechanical destruction of brain parenchyma. The most common causes are traffic, work, home and sports accidents. The incidence of cranio-cerebral traumas in industrialized countries is ~200–300/100,000 per year (1). TBI occurs biphasic with peaks during youth and later in life and is one of the most common causes of morbidity and mortality of young adults <45 years of age (1). The total European annual health care cost of TBI exceeds 33 billion € (2). The socioeconomic impact of the sequelae of TBI become evident from the large number of 57 million patients worldwide, the high unemployment rate among affected patients and the high frequency of co-morbidities (3).

The severity of TBI is classified into three degrees depending on either depth or duration of the initial posttraumatic unconsciousness. For an objective diagnosis of unconsciousness, Graham Teasdale and Bryan J. Jennett established in 1976 the so-called "Glasgow Coma Scale (GCS)" (4). The score evaluates the best response (verbal, motor, eye opening), either spontaneous or upon stimulation. A deeply unconscious patient is given a GCS value of 3 points, whereas awake, inconspicuous patients receive a score of 15 points. This simple test is applied routinely for rapid assessment of patients with brain pathologies. Severity of head injury is classified depending on the length of unconsciousness after head injuries into mild TBI (I°) with a very short (<15 sec) period with loss of consciousness, or if an accident causes loss of consciousness for more than an hour, as severe (III°) TBI. According to the GCS, severe TBIs classified patients with 3–8 points (III°), moderate TBI with 9–12 points (II°) and mild TBI (I°) with 13–15 points. 20% of adults with severe TBI show permanent neurological impairment. Approximately 1–14% of

Address reprint requests to: Winfried Neuhaus, Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria; Phone: +431427755085; FAX: +43142779551; E-mail: winfried.neuhaus@univie.ac.at

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patients with severe TBI remain in a vegetative state and 20−40% of patients die after a severe TBI due to the brain injury or secondary complications (3).

TBI damages the brain in two phases. Initial direct impact causes parenchymal damage, which become evident as hemorrhage, tissue destruction and axonal shearing. Within hours to days the primary brain damage induces a set of secondary processes on the cellular, metabolic and molecular level such as oxidative stress, inflammation and apoptosis. These processes promote the so-called secondary brain damage, an expansion of the initial mechanical brain injury in surrounding healthy tissue with pericontusional brain swelling. The emergence of cerebral edema causes a mass effect on surrounding healthy tissue, enhancing these secondary processes. Cerebral edema formation is therefore one of the main factors for the high mortality and morbidity after TBI and is the leading cause of death in more than half of all deaths after severe TBI (5).

In order to limit secondary damage after TBI, multiple studies have been conducted. Unfortunately, none has proven to be effective in the clinical setting. In order to control elevated intracranial pressure, clinical evidence is regularly screened by the Brain Trauma Foundation (BTF) and published in their guidelines (6). Due to lack of neuroprotective strategies, medical treatment focuses on general factors such as the stabilization of homeostasis, e.g., body temperature, blood pressure, oxygenation, and blood glucose levels. Currently, treatment is guided by intracranial pressure (ICP), which is measured by, e.g., use of a parenchymal probe or external CSF drainage systems. Measurement is recommended by BTF in unconscious patients and elevated ICP levels are treated with a multimodal approach employing sedation, moderate hyperventilation, hypothermia, hyperosmolar therapy, or surgical decompression by craniectomy. Although these strategies address the intracranial volume by either reduction of intracranial blood volume (hyperventilation, hyperosmolar therapy, etc.) or expansion of free space (decompression), no treatment is available, which successfully stabilizes the BBB integrity and prevents brain edema formation.

The Blood−Brain Barrier and TBI

The main components of the blood−brain barrier (BBB) are brain capillary endothelial cells (BCEC). BCECs line the intracapillary lumen. Major functions of the BBB are to maintain the homeostasis between blood circulation and the central nervous system (CNS) and to protect the CNS from bacteria, viruses, and the influx of unwanted xenobiotics. The BBB represents a physical, transport and metabolic barrier. In comparison to the peripheral endothelium, BCECs lack fenestrae and exhibit restricted pinocytosis (7). Intercellular gaps between BCECs are sealed by tight junction networks, and cell-cell contacts are supported by adherens junctions. Currently, the most important proteins contributing to tight junction formation are believed to be claudin-5 and occludin (Figure 1). The role of claudin-3 and claudin-12 and the presence of claudin-1 are still under debate and investigation (8,9). Tight junctions especially restrict the paracellular permeability of hydrophilic substances. This tightness is reflected in high transendothelial electrical resistance (TEER) values of 1000−2000 Ohm*cm^2 *in vivo* (10). It was shown that adherens junction proteins such as VE-cadherin are also important for the establishment of tight junctions (11). Highly complex transporter protein machinery controls the influx as well as efflux of compounds. A huge array of solute carrier (SLC) and ATP-binding cassette (ABC) transporter families is responsible for the regulated permeation of nutrients (glucose, amino acids), nucleotides or hormones, but also for the efflux or restricted access of waste products, neurotransmitters (glutamate) or xenobiotics. Especially, the entrance of drugs is hindered by ABC transporters such as ABCB1 (also called P-glycoprotein, P-gp), ABCG2 (also called BCRP) or the family of ABCC-transporters (also called multiple drug resistance-related proteins = MRPs). This is of particular importance with regard to the phenomenon of multidrug resistance in diseases such as epilepsy or brain tumors, but also for peripheral acting drugs that should not enter the CNS (12,13). Transcytosis can occur in a receptor- or adsorption-mediated manner, some of the relevant receptors are the transferrin or insulin receptor. BCECs also possess a significant number of enzymes, which convert entering substances in their chemical structures to reduce their permeation. Notably, a five- to ten-fold increased density of mitochondria results in increased metabolic activity in comparison to peripheral endothelial cells that contribute to the metabolic barrier properties of the BBB. Details are summarized in excellent reviews (12,14). Currently, the terms neurovascular or gliovascular unit (NVU, GVU) are used to describe that barrier properties of brain endothelial cells are regulated by cells of its microenvironment. From the CNS side, >95% of endothelial cells are ensheathed by astrocyte end feet on the CNS side and for every two to four endothelial cells a pericyte shares their basal lamina. Almost direct cellular contact and short diffusion distances for signaling molecules (neurotransmitters, growth factors, cytokines, etc.) enhance intercellular communication. Current data support the hypothesis that astrocytes are more important for upregulation of BBB-specific properties, whereas pericytes are more responsible for suppressing properties of peripheral endothelial cells (which possess increased transcytosis activity and more fenestrae) at the BBB (15). Moreover, further data also suggest influence of other neighboring cells such as microglia, oligodendrocytes and neurons on the BBB (16,17). In addition, data about blood flow and subsequent shear stress on BCECs support its immense importance for BBB functionality (18).

In several chronic and acute CNS diseases (Alzheimer's disease, multiple sclerosis, epilepsy, stroke, amyotrophic