Chapter

Role of 5-HT in Cerebral Edema after Traumatic Brain Injury

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Abstract

The pathogenesis of edema after traumatic brain injury is complex including the destruction of micro-vessels and alterations in microcirculation around the primary injury and leakage of plasma constituents into the tissue, due to permeability changes of the vessel walls. Many functional molecules like histamine, serotonin, arachidonic acid, prostaglandins and thromboxane have been shown to induce blood–brain barrier (BBB) disruption or cell swelling. It is believed that released 5-HT binds to 5-HT_2 receptors stimulating cAMP and prostaglandins in vessels that cause more vesicular transport in endothelial cells leading to serum component's extravasation. The additional amount of serotonin into the tissue due to injury maintains the state of increased vascular permeability that ultimately causes edema. Serotonin is clearly involved in early cytotoxic edema after TBI. Reduction of serotonin in the nervous tissue reduces swelling and the milder cell changes in the brain or spinal cord of traumatized rats. Inhibition of serotonin synthesis before closed head injury (CHI) in rat models or administration of serotonin antiserum after injury attenuates BBB disruption and brain edema volume swelling, and brain pathology. Maintaining low serotonin levels immediately after injury may show neuroprotection and combat various secondary outcomes that occur after traumatic brain injury.

Keywords: TBI, 5-HT (5-Hydroxytryptamine), cerebral edema, BBB permeability, brain damage, neuroprotection

1. Introduction

Traumatic brain injury (TBI), the principal cause of morbidity and mortality is a serious medical problem in people under 40 years of age. As a major cause of death, it is a major worldwide concern and due to lifetime disability it also puts a huge burden on society. [1] Despite the scale of this public health crisis, no effective TBI therapies currently exist. [2] The hope for effective treatment is derived from the fact that much of the post-traumatic damage to the injured brain is caused by a secondary injury cascade of consecutive pathophysiological events, including opening of the blood–brain barrier (BBB), formation of edema, excitotoxicity, inflammatory response activation, oxidative stress and ultimately cell death, which exacerbates the primary injury. [3] While a variety of factors lead to elevated TBI-related mortality and morbidity, the occurrence of cerebral edema with brain swelling remains the most important outcome that contributes to morbidity and mortality. [4] In the first week after traumatic brain injury, considering the prevalence of cytotoxic (or cellular) edema, brain swelling can only occur with the addition of water from the

vasculature to the cranial vault. As such, blood–brain barrier permeability control has been a subject of recent research that aims to treat brain edema. [4] Many functional molecules like histamine, serotonin, arachidonic acid, prostaglandins and thromboxane have been shown to induce BBB disruption or cell swelling. It is believed that released 5-HT binds to 5-HT_2 receptors stimulating cAMP and prostaglandins in vessels that cause more vesicular transport in endothelial cells and also leading to serum components extravasation. [5]

It is well known that serotonin (5-hydroxytryptamine, 5-HT) is involved in emotional disorders, such as depression and schizophrenia [6]. 5-HT has a role in cerebral edema after TBI [7]. Serotonin has been reported to increase nitrogenoxide (NO) tissue levels, and NO contributes to inflammation by increasing vascular permeability, which leads to edema formation [8, 9]. Activation of the 5-HT_{2B} receptor induces endothelium-dependent NO release [10]. Increased calcium levels in endothelium lead to NO formation through the eNOS pathway, followed by a cGMP-dependent mechanism to increase vascular permeability. [11] Therefore, it seems likely that 5-HT may play a significant role in edema after traumatic insults to the brain. Therefore, in the present chapter the role of endogenous 5-HT in BBB breakdown and in edema formation is discussed as a pharmacological approach to alleviate cerebral edema after TBI.

2. Pathophysiology of cerebral edema

After brain injury, secondary complications like cerebral edema are a pressing medical problem and can increase mortality to nearly 80% if severe [12]. Cerebral edema and brain swelling are estimated to account for up to 50% of patient mortality following traumatic brain injury [4]. Cerebral edema is now understood to develop in stages, where each stage is marked by distinct morphological and molecular changes [13]. Minutes after acute central nervous system (CNS) injury, cytotoxic edema or cellular swelling manifests itself. After cytotoxic edema, ionic edema, an extracellular edema that arises in the presence of an intact blood brain barrier (BBB), forms immediately. Hours after the initial insult, vasogenic edema, an extracellular edema which involves extravasation of plasma proteins manifested. [13] Neurons are considered as fragile cells and cannot survive without support from other cell types. So, in addition to provide neuroprotection, a new aim for acute brain injury research is to investigate and attenuate mechanisms of endothelial, astrocytic, and microglial dysfunction and, thereby, create an environment permissible to neuronal survival. It follows that cerebral edema, a phenomenon arising from astrocyte and endothelium dysfunction, is an important subject for fundamental research and therapeutic intervention. [13].

The term BBB refers to an organization of different cell types that separates the luminal contents of the cerebral vasculature from the brain interstitium. Brain ISF, which interacts openly with cerebrospinal fluid (CSF), is designed for neuronal activity and differs from blood serum because it includes higher levels of Cl^- and Mg^{2+} and lower concentrations of K^+, Ca^{2+} and HCO^{3-} [14]. The Virchow Robin space and the astrocyte endfeet that are part of BBB are recognised as important anatomical components of the so-called “cerebral glymphatic system” [15]. This system is designed to account for CSF movements observed in the healthy brain that can operate from the parenchyma to clear solutes such as amyloid beta and promote the transport of tiny lipophilic molecules, particularly during sleep. [15–17]

A pathological rise in the water mass contained by the interstitial space of the brain is cerebral edema. Cytotoxic edema is swelling of oncotic cells, resulting in fluid accumulation intracellular rather than extracellular and is best considered as

a precursor to extracellular ionic edema. A mass effect that exerts pressure on the surrounding shell of tissue is caused by brain swelling. The rigid enclosure of the skull magnifies this pressure rise, which puts an upper limit on the volume to which the brain can expand. It exerts mechanical forces on the skull interior as the brain swells, thereby increasing intracranial tissue pressure. Capillary lumens collapse as tissue pressure reaches capillary pressure, precipitating a feed forward phase in which the surrounding shell ischemia induces more edema development and further swelling in the next shell. [18]

Two key theories exist about the immediate source of the new water mass required for brain swelling. In one theory, water, driven by osmotic forces, travels from the capillary lumen into the parenchyma and is transmitted through capillary endothelial cells. In support of the first theory, local blood perfusion status is closely correlated with the formation of ionic edema. [19] Magnetic resonance imaging (MRI) reveals that edema is first observed in regions of peri-infarction that are actively perfused in human stroke. [20] However, acceptance of this theory is not universal, as there are doubts about the levels of expression of widely cited molecular mechanisms for influx of ions and water via endothelium in the brain [21]. A recent explanation of the glymphatic system has led to the formulation of a second theory, in which CSF is the immediate source of water and ions. In this theory, swelling occurs when the influx of CSF into the parenchyma is increased and/or interstitial fluid (ISF)efflux is impaired, a condition that precipitates the parenchymatic relative accumulation of ISF [21]. The two theories do not account well for the formation of vasogenic edema.

Cytotoxic edema is a premorbid cellular process also known as cellular edema, whereby extracellular Na^+ and other cations enter into neurons and astrocytes and accumulate intracellularly due to failure of energy-dependent mechanisms of extrusion. This process takes place following CNS injury in all CNS cell types, but is especially prevalent in astrocytes. Astrocyte swelling tends to be a response of astrocytes to injury and occurs rapidly following a number of forms of CNS injury, including ischemia, trauma, hypoglycemia, epileptic status, and fulminant hepatic failure. [14] In the development of cerebral edema and swelling, cytotoxic edema is an important initial stage, as it generates the driving force for the influx of ionic and vasogenic edema, which induces swelling. As a consequence of primary active transport or secondary active transport, osmolite cellular influx may occur. A continuous supply of adenosine triphosphate (ATP) is needed for primary active transport to provide energy for "pumps" such as the Na^+/K^+-ATPase and Ca^{2+}ATPase. [13] Secondary active transport utilises the potential energy stored in transmembrane ionic gradients that was previously generated through primary active transport. Secondary active transporters include ion channels and cotransporters such as the $Na^+/K^+/Cl^-$ co-transporter (NKCC) [1, 22] and the Na^+/Ca^{2+} exchanger. After many types of CNS injury, intracellular ATP becomes depleted and due to that mechanism independent of intracellular ATP, like secondary active transport, are more likely to be involved in the formation of ionic edema. [13] NKCC1 is constitutively expressed by astrocytes in all region of the adult brain [22–24] In vitro experiments using cultured primary astrocytes is shown that NKCC1 leads to cell swelling in conditions of high extracellular potassium. [25, 26] In vivo, swelling is decreased by the NKCC1 inhibitor bumetanide after trauma and ischemia [27–29].

Acute CNS injury activates a program of molecular changes in the neurovascular unit before and after transcription that leads to the development of endothelial "permeability pores" and subsequent loss of BBB integrity. Based on the key substances undergoing transcapillary motion, progressive endothelial dysfunction can be organised into three stages, i.e. ionic edema, vasogenic edema, and hemorrhagic conversion. [13]

Vasogenic edema is a type of extracellular edema characterized by BBB breakdown, in which a pore of transendothelial permeability develops that allows the interstitial brain compartment to extravasation of water and plasma proteins such as albumin and IgG. Capillary structural integrity, unlike hemorrhage, is maintained during vasogenic edema in such a way that erythrocyte passage is prevented. [30] It is thought that the three phases of endothelial dysregulation occur sequentially, although the speed of change between phases possibly depends on the form and severity of injury. In addition, since many etiologies of brain endothelial dysregulation and cerebral edema are focal in nature, brain tissue typically displays a complex spatiotemporal pattern of the various stages of endothelial dysregulation. Significant gaps still remain in our understanding of how specific proteins contribute to cerebral edema. [13]

3. Serotonergic role in development of cerebral edema

In many brain disorders, edema is a severe complication, including traumatic injury. Traumatic brain edema pathogenesis is complex and involves physical disruption of microvessels, microcirculatory changes in and around the primary injury, and changes in the permeability of the vessel walls that contribute to plasma constituents leaking into the tissue. [31] There are reasons to assume that many of these events are caused by a variety of chemical mediators, such as biogenic amines, arachidonic acid, leucotrienes, histamine and free radicals, that are released or activated in and around the primary lesion [32]. However, the role of serotonin (5-hydroxytryptamine, 5-HT) is not well understood in traumatic brain edema. In multiple neurological disorders and in pathological conditions, several lines of recent evidence suggest a presumptive function of this amine. [7] Major changes in the synthesis of serotonin occur in important brain injuries such as stroke, ischemia and trauma, as well as in experimental cold injury lesions and other neurological diseases. [7] Increased serotonin content occurs after traumatic brain insults in the walls of the cerebral vessels, cerebrospinal fluid and brain. [5] In a wide range of psychiatric disorders and mental disturbances, irregular serotonin levels in the blood and brain have been identified. [33] In cerebral vessels, serotonergic receptors are present and intracarotid, intravenous or intracerebroventricular serotonin infusion substantially affects the cerebral circulation and metabolism as well as increasing the permeability of the blood–brain barrier (BBB) [7, 32, 34] Therefore, various studies were conducted to examine the function of endogenous 5-HT in BBB breakdown, edema formation and early cellular changes in experimental models of traumatic brain injury. Therefore, it seems probable that 5-HT could play an important role in edema formation and cellular changes following traumatic insults to the brain.

Studies show that endogenous depletion of 5-HT before acute insult to the brain substantially thwarts the production of edema and early cellular changes, suggesting that this amine plays an important role in the pathophysiology of traumatic brain injury [35]. Clearly, physical damage to the brain can initiate a cascade of biochemical and structural events in and around the primary injury. [36] Edema is one of those secondary events that may aggravate a primary injury, and studies suggest that serotonin could be involved in edema-causing micro vascular reactions [7]. Serotonin is present in many neuronal pathways arising from the nuclei of the dorsal raphe and leptomeninges mast cells and in blood platelets. [33] Changes in the concentration of serotonin most possibly occur during the progression of the injury. At the same time as edema is produced, additional quantities of serotonin may be brought in from the blood or from neurons. However, biochemical determinations suggest a rise in the

serotonin content of the traumatized brain. [37] Serotonin is a powerful chemical micro vascular response mediator to cerebral edema. [32] Results of para-chlorophenylalanine (pCPA) pretreatment before trauma induction are consistent with the notion that serotonin plays a role as a vascular permeability-increasing compound that contributes to early edema. [7, 38] Para-chlorophenylalanine (pCPA), acts as a selective and irreversible inhibitor of tryptophan hydroxylase, which is a rate-limiting enzyme in the biosynthesis of serotonin. This is further demonstrated by the fact that the degree of cell changes in the periphery of the initial lesion is lower in pCPA pretreated rats than in non-treated animals with the same type of injury. [7] Therefore, it seems obvious that the decrease in the content of serotonin in the nervous tissue is somehow reflected in the decreased swelling and milder changes in the brain of traumatized rats. Nevertheless, apart from the effects of serotonin, arachidonic acid release, prostaglandins and thromboxane can synergistically contribute to edema formation.

The microdialysis technique was used in the popular carotid artery for intra-arterial recordings. This new application was found to be a genuinely acceptable and effective method that allows direct measurements of HPLC plasma serotonin without any further extraction process [39]. Studies show a significant increase in downstream plasma serotonin concentrations in response to acute non-occlusive common carotid artery thrombosis (CCAT) that appears to be caused solely by endothelium photochemical and not photo thermal impact. As a mediator of blood brain barrier disturbance and/or irregular cerebral blood flow and/or neuronal impairment in ischemic stroke and transient ischemic attacks (TIA's), the rise in serotonin may be of significant importance [39].

3.1 Role of 5-HT2 receptors in formation of edema

5-HT_2-receptor antagonists, ketanserin [40] and LY 53857 [41] prevent capsaicin-induced mouse ear edema. [42] Antagonists of the 5-HT_1-receptor and 5-HT_3-receptor ICS 205–930 and MDL 72222 [43] respectively, had no effect on edema caused by capsaicin. [42] The findings clearly indicate that 5-HT is partially involved in the development of edema via 5-HT_2 receptors. 5-HT is known to induce plasma extravasation by direct action on rat microvasculature [44] and to produce vasodilation on peripheral blood vessels through 5-HT_1 receptors [44] A recent study indicated that endogenous nitric oxide, in addition to 5-HT receptors, is involved in a 5-HT-induced increase in vascular permeability in mouse skin. [45] In addition to activation of 5-HT_2 receptors, 5-HT plays a role of releasing neuropeptides including SP as the second mediator of increased vascular permeability at inflammatory sites. [46] Mediators like SP, bradykinin and prostaglandins, on the other hand, can release tachykinins from primary afferent terminals. [47] Many functional molecules like histamine, serotonin, arachidonic acid, prostaglandins and thromboxane have been confirmed to induce BBB disruption or cell swelling. It is believed that released 5-HT binds to 5-HT_2 receptors that stimulate cAMP and prostaglandins in vessels that cause more vesicular transport in endothelial cells and leading to serum components extravasation. The additional amount of serotonin into the tissue due to injury maintains the state of increased vascular permeability that ultimately causes edema. Changes in serotonin concentration were detected early after focal traumatic injury to the rat spinal cord and were associated with edema formation and alterations in blood flow. [35] Compared to controls, the serotonin concentration in the traumatised section increased more than 100 percent in five hours after the injury. The water content of the traumatised section estimated 5 h after the injury was also gradually increased whereas para-chlorophenylalamine, serotonin synthesis inhibitor, impeded the elevation in water content measured 5 h after the trauma. [35]

3.2 Effect of antibodies to serotonin in closed head injury

Closed head injury (CHI) is a serious clinical issue that leads to immediate death for most patients. [48] Swelling of the brain in a closed cranial compartment that results in compression of the brain's vital centers tends to be primarily responsible for instant deaths. [49] CNS microhemorrhage, blood–brain barrier (BBB) permeability breakdown, and brain edema development, alone or in combination, are primarily responsible for cell damage and long-term neurodegenerative changes following CHI. [37, 50, 51] Unfortunately, so far, no effective validated therapies are accessible. Efforts to understand the molecular mechanisms of early pathophysiological events in an animal model of CHI are therefore urgently required to explore the possible therapeutic potential of different neuroprotective agents in order to reduce the development of edema and cell death.

In brain or spinal cord injuries increased plasma and brain levels of serotonin following CHI is seen in previous studies. [50, 51] There was a strong link between this rise in tissue serotonin levels and BBB breakdown and edema formation. [52] This is further reinforced by the fact that previous inhibition by p-chlorophenylalanine (pCPA) of serotonin biosynthesis greatly attenuated the formation of brain edema, BBB damage, and cell injury in brain and spinal cord injury. [50, 51, 53] Taken together, these findings strongly indicate an important role for serotonin in CNS trauma pathophysiology. Subsequent trials of CNS damage using serotonin receptor blocker drugs showed controversial results, however. [34, 54, 55] Blocking of 5-HT_{2c} and 5-HT_{1A} serotonin receptors improves cognitive function and reduces the formation of brain edema at low doses. [52, 56, 57], other serotonin receptor antagonists, in fact, exacerbated the pathological outcome following brain injury [58, 59] Thus, further research is needed into the role of serotonin receptors in mediating brain pathology in CNS injuries. Since serotonin has more than seven receptor types with several subtypes of receptors [52, 56, 58] There can be no clear view on this topic of amine involvement using a few unspecific receptor antagonists. In addition, the dosage response and time schedule of drug therapy can further affect the final outcome. [60]

Results from studies demonstrate that intracerebroventricular administration of monoclonal serotonin antibodies either 30 min before or 30 min after CHI induced profound neuroprotection. Therefore, after CHI, marked decreases in BBB disruption, brain edema formation, and cell injury were noted in serotonin antiserum-treated animals. Such novel results indicate that early intervention in CHI with serotonin antiserum is neuroprotective. [60] Taken together, these findings suggest the active participation of this amine during the early stages of CHI, in the cellular and molecular pathways of brain edema formation and BBB breakdown. The neuroprotective effects of antiserum serotonin in CHI are dose-dependent. This indicates that to induce neuroprotection, enough serotonin antiserum is required to block in vivo brain serotonin. On the other hand, when given 60 min after CHI, even a high concentration of serotonin antiserum was ineffective. This means that serotonin involvement is important for brain pathology within 30 minutes of CHI. [60]

Elevation in plasma and brain serotonin concentration by intravenous injection of serotonin (10 to 20 g/kg/min) in animals without CHI disrupts the BBB function within 10 min. [52, 59, 60]. This effect of the serotonin on BBB interruption is reversible. To measure BBB disruption, many approaches are used. Extravasation of Evans blue (EB) dye is the most commonly used procedure. Normally, Evans blue does not move through the BBB and hence its presence in brain tissue suggests permeability alterations. Thus, when the same dye was administered 2 to 3 hours after serotonin administration, BBB permeability to Evans blue dye was no longer observed. This means that the dosage and length of exposure to serotonin

play a significant role in development of brain pathology. This principle is further confirmed by the prevention of BBB breakdown by previous serotonin synthesis inhibition, which attenuated an increase in plasma and brain serotonin in CHI. [60]

BBB permeability breakdown is associated with vasogenic brain edema formation and cell injury [61–63]. Protein leakage from the vascular compartment via the blood–brain interface into the neuronal microenvironment will alter osmotic balance. A change in osmotic balance will allow the bulk flow of water from the vascular compartment to the cerebral compartments. Furthermore, the release of neurochemical mediators of brain edema, e.g. serotonin, prostaglandin, histamine and neuropeptides, via particular receptor-mediated pathways, will further affect water transfer from blood to the brain. These neurochemicals also cause the BBB process to break down. This hypothesis is consistent with a close relationship between the development of brain edema, the amount of serotonin and BBB disruption in CHI. [60]

3.3 Serotonergic receptors in brain edema

Tissue collected after ischemic insult in gerbils showed two binding sites for ketanserin, one with a lower and one with a higher affinity than that found in sham-operated and ischemic animal brains. Ketanserin, a quinazoline derivative, is a selective 5-HT2 serotonin receptor antagonist with weak adrenergic receptor blocking properties. The results strongly suggest that the properties of binding sites for the S2 receptor are altered in ischemia-induced cerebral edema [64]. The demonstrated regulation of the binding sites of ketanserin appears to correlate with the observed attenuated metabolic rate (= increased release) but not with the abnormal brain 5-HT levels. Studies indicate that the variations in 5-HT ischemic patterns are most likely related to the type and model of ischemia and/or brain structure examined, as well as to the 5-HT detection system used [64] However, in the brains of gerbils subjected to 15 min bilateral carotid artery occlusion without recirculation, 5-HT metabolism is unquestionably disturbed. [65–67] Therefore, there may be numerous explanations for the lack of apparent changes in the kinetic characteristics of 5-HT_2 receptor binding sites, especially if the presynaptic region is considered to be the primary site of the ischemically disrupted 5-HT pathway. The most critical of these are: (a) the insufficient lapse of time (15 min of ischemia) and/or the absence of recirculation required for the production of post-synaptic changes; and/or (b) the presence in the subcellular compartment of altered 5-HT_2 receptor properties obscured by the analysis of the entire cortical homogenate rather than the relevant fraction [64].

In neuronal and/or glial and/or vascular postsynaptic membranes, the modified 5-HT_2 receptors may be localized. Desensitization and hypersensitization of the receptor sites are demonstrated by the detection of 5-HT_2 postsynaptic binding sites with lower and higher affinities (indicated by apparent higher K_D and lower K_D) after 1 h of recirculation than those seen in the ischemic and control cortex. Due to increased release, reduced uptake and reuptake of 5-HT in the presynaptic regions, this could be the result of inappropriately accessible 5-HT at the postsynaptic receptor sites. [64] In general, this phenomenon is consistent with the well-known agonist-specific desensitization of high levels of hormones and neurohormones exposed to cell membranes, whereas their depletion results in supersensitization [68]. In addition, in the recovery period (recirculation of 1 and 2 h), the observed 5-HT_2 binding sites with a higher affinity (lower K_D) than those seen in ischemic and control brains may indicate either an unmasked pre-existing site or an additional binding site. It can be assumed that the existing disruptions of the 5-HT pathway and its adverse effects are not limited to the presynaptic, but also include the postsynaptic subcellular compartments, based on the observed changes in the properties of S2 receptor binding sites. [64]

In addition, it is conceivable that the presynaptically released 5-HT into the synaptic cleft is also able to directly impact the membrane. In this way, unmetabolized 5-HT overflow can lead to increased permeability of the membrane, allowing for more pronounced passive ion transfer and water accumulation in the cells [64]. This inference is confirmed by the additional increase in Na^+ observed, a decrease in K^+ concentration and a decrease in Na^+-K^+-ATPase activity at the time of most marked cell swelling. In particular, the concomitant occurrence of changes in the kinetic properties of S2 receptors and the activity of Na^+K^+-ATPase is of concern, since an increase in PGF2a levels was also observed after the same period of ischemia and recirculation. 5-HT can stimulate the development of PGF_{2a}, since this amine increases the formation of PGF1a in cultured cerebrovascular elements. Nevertheless, it remains to be clarified if 5-HT affects directly or indirectly Na^+K^+-ATPase operation. [64] list Nevertheless, at the time of the most conspicuously increased cellular water in the brain of gerbils subjected to ischemia and recirculation, the observed alteration of 5-HT_2 receptors strongly supports the argument of 5-HT involvement in edema formation and/or progression [64].

4. Neuroprotective role of serotonin after TBI

4.1 In cerebral ischemia

The severity of secondary TBI mechanisms depends on the severity of the injury or the primary insult location. Reductions in cerebral blood flow [69, 70] have been reported to exceed ischemic levels in conditions of extreme TBI. Cerebral ischemia is therefore addressed as one secondary cause of injury that may be involved in brain trauma. [69, 71] There is a massive increase in the concentration of both excitatory and inhibitory neurotransmitters in the extracellular space during cerebral ischemia [72–75]. It has been proposed that over-excitation of neurons triggered by excitatory amino acid neurotransmitters plays a major role in the pathogenesis of ischemic neuronal destruction [76]. Glutamate induces an influx of Ca^{2+} and Na^+ into the neuron by acting on N-methyl-D-aspartate (NMDA) and non NMDA receptors. The neuronal membrane depolarizes strongly and can allow Ca^{2+} to reach the cell through additional pathways. These events can lead to a neurotoxic accumulation of intracellular $Ca^{2+.}$ [77] In addition to glutamate antagonists, agents that induce neuronal membrane hyperpolarisation may be able to reduce the influx of Ca^{2+} via these ionophores and may exert neuroprotective effects. 5-HydroxytryptaminelA (5-HT_{1A}) receptors through Ca^{2+}-independent K^+-conductance mediate an inhibitory, hyperpolarizing effect on cortical and hippocampal neurons. [78–80] It has been shown that 5-HT_{1A} receptor agonists imitate 5-HT's hyperpolarizing activity on the resting membrane potential, increase the firing threshold, and decrease the firing rate of hippocampal CA_l, cortical, and dorsal raphe neurons [81] The complexity of 5-HT's function in cerebral ischemia is probably due to the multiplicity within the brain of 5-HT receptors and their distinct distribution and densities. 5-HT_{1A} receptors mediate the inhibitory effect on neurons, as mentioned above. However, 5-HT also stimulates hippocampal and cortical neurons via 5-HT_2 receptors. [80, 82]

4.2 In neurocognitive and neuropsychiatric disorders following traumatic brain injury

Due to variable diagnostic criteria, the prevalence of post-TBI depression varies from 6–77% [83], and up to 53% in the first year after injury [84]. The association between TBI and the development of neuropsychiatric disorders is

well documented. [85, 86] Disruption of the serotonergic system is one unifying factor that underlies acquired neuropsychiatric disorders following TBI. As the blood–brain barrier cannot be crossed by serotonin, synthesis must occur de novo in the brain. The shearing of brain stem axons during TBI effectively interferes with pontine and medullary serotonergic projections, resulting in decreased serotonin metabolism and production. [87–90] Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant agents which inhibit serotonin reuptake by presynaptic cell monoamine transporters and increase extracellular concentration of serotonin, enabling increased serotonin availability in the synaptic cleft and increase activation of postsynaptic serotonergic receptors, resulting in increased synaptic signaling. SSRIs are involved in regulation of neuronal cell survival and neuroplasticity for the treatment of psychiatric disorders, including depression, obsessive–compulsive disorder, bulimia, and panic disorder. [91] Serotonin modulates mood, arousal, emotion, and working memory, and thus constitute SSRIs an attractive, treatable, and potentially long-term pharmacological intervention for neurocognitive and neuropsychiatric deficits post-TBI. [92] Consequently, the judicious use of SSRIs in post-TBI depression treatment is of great importance and impact.

5. Pharmacological interventions after TBI related to serotonin

A growing number of patients are surviving with residual neurological impairments due to improvements in the treatment of head trauma. A commission of the National Institute of Health reports that there are currently 2.5 to 6.5 million Americans with TBI-related disabilities [93]. Information from various disciplines and professions beginning at the time of injury and continuing through the recovery process is required for successful treatment of TBI. In both the sub-acute (less than 1 month post TBI) and chronic (more than 1 month post TBI) stages, pharmacotherapy is used. Selective serotonin reuptake inhibitors (SSRIs) have been found to be helpful in the treatment of behavioral syndromes in patients with TBI, especially in the sub-acute recovery phases [94], but also in chronic settings. Most studies indicate that SSRIs enhance neurobehavioral, neurocognitive, and neuropsychiatric deficits, especially agitation, depression, psychomotor retardation, and recent memory loss, but most of the information comes from non-randomized studies. Similarly, bupropion boosts the levels of both dopamine and norepinephrine and is a weak serotonin reuptake inhibitor. This agent has been effective in treating restlessness at 150 mg per day [95] .For anxiety, depressed mood, and deficits in psychomotor pace and recent memory, sertraline administered at an average dose of 100 mg daily for 8 weeks was found to be beneficial but shorter treatment durations have shown no benefit [94]. There was a strong link between the rise in tissue serotonin levels and BBB breakdown and edema formation [52]. This is further reinforced by the fact that previous inhibition by p-chlorophenylalanine (pCPA) of serotonin biosynthesis greatly attenuated the formation of brain edema, BBB damage, and cell injury in brain and spinal cord injury [53]. Blocking of 5-HT_{2c} and 5-HT_{1A} serotonin receptors improves cognitive function and reduces the formation of brain edema at low doses [52, 56]. Thus, 5-HT_2 receptor functions need to be explored more in the development of cerebral edema and this can be used as pharmacological intervention to reduce cerebral edema.

6. Conclusion

Due to permeability changes in the vessel walls, the pathogenesis of edema after traumatic brain injury is complex, including disruption of micro vessels and

changes in microcirculation around the primary injury and leakage of plasma constituents into the tissue. To cause BBB disruption or cell swelling, several functional molecules such as histamine, serotonin, prostaglandins and thromboxane are involved. The 5-HT released is believed to bind to 5-HT2 receptors stimulating cAMP and prostaglandins in vessels that trigger further vesicular transport in endothelial cells, leading to extravasation of the serum portion. Serotonin is involved in early cytotoxic edema after TBI. Reduction of serotonin in the nervous tissue is shown to reduce swelling and the milder cell changes in the brain or spinal cord of traumatized rats. Inhibition of serotonin synthesis before CHI in rat models or administration of serotonin antiserum after injury attenuates BBB disruption and brain edema, volume swelling, and brain pathology. BBB disturbance and brain edema, volume swelling, and brain pathology are attenuated by inhibition of serotonin production before CHI in rat models or the administration of serotonin antiserum after injury. Immediately after injury, maintaining low serotonin levels can demonstrate neuroprotection and fight various secondary outcomes that occur after traumatic brain injury.

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