Journal of Surgery and Trauma 2019; 7(1):3-14.
jsurgery.bums.ac.ir

REVIEW ARTICLE

Effects of endocannabinoid system, synthetic and nonsynthetic cannabinoid drugs on traumatic brain injury outcome: a narrative review

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Received: August 29, 2018 ***Revised: December 09, 2018*** ***Accepted: February 19, 2019***

Abstract

Traumatic brain injury (TBI) is the leading cause of morbidity and mortality worldwide. The initial injury is followed by a series of secondary processes that can further harm the injured brain and worsen the outcome. The endocannabinoid system (ECS) consists of ligands, such as anandamide and 2-arachidonoyl-glycerol (2-AG), receptors (e.g., Cannabinoid receptor type 1 and Cannabinoid receptor type 2), as well as transporters, and enzymes. Dexanabinol (HU-211) is a synthetic cannabinoid with cerebroprotective effects devoid of cannabimimetic effects, which exhibits the pharmacological properties of *N*-Methyl-D-aspartate receptor antagonist. The increase in the brain levels of endocannabinoids in the pathogenic events of brain injury suggests that this system plays a role in compensatory repair mechanisms. In recent year, the therapeutic effects of cannabinoid manipulative drugs have been numerously studied through the manipulation of the ECS in TBI. Therefore, the literature review was performed to assess the therapeutic effects of ECS manipulation, cannabinoid-derived drugs, and HU-211 in traumatic brain injury pathology. The ECS possesses promising effects in the treatment of diverse TBI pathologies through releasing endogenous ligands and changes in cannabinoid receptors activity or both. Preclinical studies suggest that the ECS has many targets for therapeutic agents that might help decrease TBI pathologic effects and should be considered for developing novel drugs. Furthermore, more clinical trials with larger populations and more extended follow-up periods should be performed for a better understanding of the effects of ECS manipulative drugs.

Key words: Brain injuries, Cannabinoids, Cannabinoid receptors, Endocannabinoids, HU 211, Traumatic

Introduction

Traumatic brain injury (TBI) is defined as "an alteration in brain function or other evidence of brain pathology caused by an external force" (1). The diagnosis in most cases is obtained through the evaluation of clinical symptoms, neurological signs, as well as neuroimaging findings (2). The TBI is categorized as mild, moderate, or severe based on 1) the initial Glasgow Coma Scale (GCS) score (A GCS score of 13-15 denoting a mild TBI, GCS score of 9–12 showing a moderate TBI, and GCS score of 3–8 demonstrating a severe TBI) and 2) the duration of loss of consciousness (LOC) or coma, as well as the duration of posttraumatic amnesia (PTA). In moderate to severe TBI, the patients tend to have a more prolonged LOC or coma and sustain PTA symptoms for a longer period (2).

The TBI-induced alterations in brain functions can lead to many symptoms, including the loss or decline of consciousness, amnesia for events immediately after the injury or before it (retrograde), neurological deficits, such as paralysis or weakness, spasticity, poor balance,

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[DOI: 10.32592/Jsurgery.2019.7.1.101]

visual changes, dyspraxia, paresis/plegia, sensory impairment, aphasia, and mental status changes at the time of the injury (e.g., confusion, disorientation to time and location, and slow thinking,) (3).

The TBI is a significant cause of morbidity and mortality worldwide. The overall worldwide incidences of TBI are 80% (mild), 10% (moderate), and 10% (severe). Only in the United States, over 1.7 million people suffer from TBI every year with over 50,000 deaths and at least one-third of survivors facing long-term disabilities (4-6). In 2012 In Europe, TBI was responsible for over 37% of all deaths related to injury (7). The highest rate of mortality due to brain injury occurs in the population older than 65 years of age. The overall rate of TBI in men is 29% higher than that in women (8). In cases of severe head injury, brain damage sometimes is immediate and irreversible.

The TBI is associated with complex pathophysiologic processes demonstrated as two types, including primary and secondary injury. Mechanical forces that physically disrupt the brain tissue itself are called primary injuries. Secondary injuries occur hours and days after the primary injuries and consist of diverse pathophysiologic processes and phenomena, such as hypoperfusion, cellular dysfunction, oxidative injuries, and disruption of blood-brain barrier (BBB) (9).

One of the central elements in the pathogenesis of secondary injury is brain edema. Elevated intracranial pressure (ICP) and decreased cerebral perfusion pressure are mainly due to brain edema (10). There are other processes that cause further damage in TBI. One of these processes is a phenomenon known as excitotoxic injury, which is the overload of excitatory amino acids, such as glutamate and aspartate in the extracellular fluid and cerebrospinal fluid leading to acute neuronal and astrocytic swelling, as well as delayed cellular damage, or cell death via cellular necrosis and apoptosis (11).

An increase in the severity of TBI is often associated with several other injuries. These joint injuries can directly affect secondary injury and the associated pathology. The results of some studies showed that the combination of TBI and hemorrhagic shock could cause more hippocampal damage, compared to just TBI, a condition which is associated with increased secondary ischemia (12-15). In the chronic period after TBI, there are multiple neurotransmitter deficits and cellular dysfunction. Brain in the chronic period after TBI is responsive to neuroplasticity, repair, and recovery.

The resolution of cerebral edema and regulation of blood flow take place in the early phases of TBI recovery. Synaptic plasticity, axonal sprouting, and cortical reorganization occur in the reversal process of diaschisis, which takes place after the early phases of TBI recovery (2). Proper rehabilitation strategies and pharmacologic interventions can manipulate late recovery (2, 16-18). The TBI is associated with direct and indirect costs. Direct costs involve the financial requirements for medical care, whereas indirect costs refer to those associated with the loss of productivity in individuals suffered from TBI, the family members that take care of them, and the costs of reduced participation in complex leisure or recreational activities (16, 19).

It has been reported that TBI patients suffer from at least one issue in the next year after their hospitalization (20). Over the past few decades, a better understanding of the TBI pathophysiology has helped develop new management guidelines and treatment paradigms that result in better clinical outcomes. However, nowadays, the treatments aim at limiting the neurochemical cascade associated with secondary brain injury. However, in the developed countries, a significant drop from 50% to 20-30% in mortality rate following severe TBI has been achieved through all efforts over the past three decades (21).

Therapeutic protocols in this regard are mainly physiological monitoring and support, performing surgical intervention when needed, as well as medications, such as mannitol, hypertonic saline, sedatives, and anticonvulsants (22). Decompressive craniotomies also have recently improved survival rate; however, the ongoing rage debate in applying this procedure is which patients are candidates for this procedure and what is the appropriate timing (23, 24).

“Cannabinoid” refers to a set of naturally occurring aromatic hydrocarbon compounds in Cannabis sativa (25). Nonetheless, today, it refers to a broad set of chemicals that their pharmacological actions or structures closely mimic those of plant-derived cannabinoids (26). Two types of cannabinoid receptors have been identified so far, including cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2).

The endocannabinoid (ECS) system consists of the ligands, such as anandamide and 2-arachidonoyl-glycerol (2-AG), receptors (e.g., CB_1, CB_2, possibly the transient receptor potential cation channel subfamily V member 1, and G protein-coupled receptor 55), transporters and enzymes, which are responsible for the synthesis (e.g., N-acyl-phosphatidylethanolamine phospholipase D, diacylglycerol lipase) and

[DOI: 10.32592/Jsurgery.2019.7.1.101]

degradation of these lipid mediators (i.e., fatty acid amide hydrolase and monoacylglycerol lipase] (27, 28).

There are three predominant categories of cannabinoids that are currently in use, including A) plant-derived phytocannabinoids (29), B) synthetically-produced cannabinoids (30) or recreational drugs (31), and C) endogenous cannabinoids (Anandamide) (32) and 2-AG (33)). The ECS has several functions in the brain under both physiological and pathological conditions. Anandamide (32) and 2-AG (33), which are produced in the brain as primary ligands, activate both CB_1 and CB_2. The 2-AG acts as a high efficacy agonist at CB_1 and CB_2 , while anandamide behaves as a partial agonist (34).

Endogenous ligands are responsible for the functional selectivity of the ECS. Neurotransmitter systems in the body traditionally generate the differential activation of signaling pathways via the activation of receptor subtypes using one neurotransmitter (35). However, in the ECS, the endogenous ligands of ECS receptors are responsible for such signaling specificity. Most of the psychomimetic effects of cannabis are mediated via a CB_1 and its main psychoactive constituent, tetrahydrocannabinol (THC), as well as many other central nervous system (CNS) active cannabinoids. The types and location of targeted cells determine the outcome of cannabinoid receptor signaling (26).

The neurons in CNS areas, such as the cerebral cortex, hippocampus, and caudate putamen, are where CB_1 are predominantly expressed (26, 36). On the other hand, CB_2 are mainly expressed in nonneuronal cells, such as immune cells, microglia in the CNS, macrophages, monocytes, CD4C and CD8C T cells, as well as B cells in the periphery (37). Although these receptors produce no psychoactivity, they are expressed on neurons but to a much less extent than CB_1 (38). The activation of CB_1 and CB_2 attenuates the inflammatory response by inhibiting the release of pro-inflammatory mediators, decreasing leukocyte chemotaxis, and extravasation into the brain parenchyma (39).

The CB_2 receptor agonists also decrease cytochrome-C release, inhibit apoptosis, and exert anti-inflammatory effects in a broad range of animal models (40, 41). The heterogeneous distribution of CB_1 and CB_2 throughout the brain and periphery probably is the reason that they impact a wide variety of physiological and psychological processes, such as memory, anxiety, and pain perception (42), many of which are influenced by TBI. It has been well-documented that pathogenic events, such as epileptiform seizures and neuronal excitability, due to the events, including trauma, significantly activate the ECS (43). Because the ECS is activated in response to such events, it can be suggested that it is part of the brain's compensatory repair mechanism mediated via CB receptor signaling (44).

The main strategy for investigating the potential neuroprotective effects of ECS in TBI animal models is via enhancing ECS signaling with selective amplification of anandamide and 2-AG levels by pharmacological inhibitors for ECS catabolic enzymes (26). Dexanabinol (HU-211) is a synthetic nonpsychotropic cannabinoid (45) that act as a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist (46). Moreover, it has antioxidant (47) and anti-inflammatory properties (i.e., TNF-α blocking) (48). It has been shown that HU-211 is effective in some animal models of traumatic and ischemic brain injury without any signs of overt toxicity at pharmacologically relevant doses (49, 50).

Drug therapies for TBI are yet to be proven and once reaching the clinical trials, there are many transitional problems (51-53). The therapeutic strategy of few drugs used in TBI is towards the manipulation of endogenous systems that are present and active from the beginning of the injury process. The ECS has a vast and diffuse area for effectiveness, and these features give the ECS a significant power to protect the CNS against pathologic processes.

The complicated pathology of TBI and the existence of any drugs for its definite cure have emerged numerous studies to examine new therapeutic strategies based on the manipulation of the ECS. Considering these, it was decided to review these scientific pieces of literature to answer some questions, such as A) To what changes do the modifications in a specific part of the ECS system relate in TBI pathologies?, B) Whether the observed effects in preclinical studies are present in the clinical studies?, C) What complications are associated with the drugs that modify the ECS system and whether they are safe for the human use?, and D) What do these performed studies lack and what has to be considered in future studies to obtain more strong evidence for determining new therapeutic strategies for TBI considering the ECS modification?

Methods

The authors of this study tried to become close to the steps of a systematic review; however, they do

[DOI: 10.32592/Jsurgery.2019.7.1.101]

not claim for performing a systematic review. The literature search was carried out using databases and search engines listed as PubMed, Scopus, Google Scholar, ScienceDirect, and Cochrane Library between 1990 and 2018. The literature search was performed using the keyword 'traumatic brain injury' in conjunction with each of the following keywords, including 'endocannabinoid system,' 'cannabinoid,' 'dexanabinol,' and 'cannabinoid-derived drug.' Original research articles and review articles in the English language were included.

Moreover, the articles in other languages with English abstract were included if needed. Other types of articles were excluded, such as the letters to editor, commentary, book review. Furthermore, the articles that were not published yet were excluded. A manual search in the reference sections of relevant review articles was also performed to identify additional studies. Most of the articles were included for final consideration. Records were firstly refined based on title and abstract. Then the remained articles were assessed based on the full texts. Finally, based on the quality appraisal of remained articles using Critical Appraisal Skills Program checklists, rigorous articles were chosen for final analysis.

Endocannabinoid system

Preclinical Studies

The CB_2 has shown a significant and endogenous role in regulating inflammation. Initial traumatic insult induces an inflammatory response that leads to neuronal damage. In a study carried out by Amenta et al. (54), synthetic selective CB_2 receptor agonists (i.e., 0-1966 and JWH-133) and a selective CB_2 receptor antagonist or a vehicle solution were used in an experimental model of TBI in rats to investigate the effects of CB_2 stimulation, blockade, and deletion on the neurovascular inflammatory responses to TBI.

Treatment with CB_2 receptor agonist attenuated tumor necrosis factor-alpha (TNF-α) protein levels and increased inducible nitric oxide synthase (iNOS) mRNA expression, while the genetic deletion of CB_2 resulted in substantial increases in iNOS expression. The CB_2 stimulation ameliorated posttraumatic inflammation and protected the neurons, while the blockade or deletion of the CB_2 increased the inflammation. The 2-AG is an endocannabinoid and an endogenous receptor agonist of CB_1 identified both in the periphery and brain.

Reactive oxygen species (ROS) and TNF-α are major contributors to the pathophysiology of brain injury. Brain edema leads to an elevation in intracranial pressure; therefore, measuring intracranial pressure and water content can be applied to determine the severity of brain edema. A study reported that 2-AG suppressed the formation of ROS and TNF-α by murine macrophages in vitro after stimulation with lipopolysaccharide (55). In another study (56), synthetic 2-AG was administrated 15 min after the experimental TBI in mice. The results showed that the levels of endogenous 2-AG were significantly increased, and the treatment with 2-AG reduced brain edema by 50%.

The clinical status of the animals was evaluated by testing motor and behavioral functions 1 and 24 h after the injury. The 2-AG treatment resulted in a good and fast recovery within 24 h after the injury, although the evaluations on the following days showed no significant improvement. Neuronal cell death was evidenced by the infarct volume around the site of injury, which was reduced by 2-AG treatment. Moreover, 2-AG treated animals showed a lower loss of neurons, compared to vehicle-treated animals.

Finally, to confirm that 2-AG effects were mediated via a CB_1, the administration of a CB_1 receptor antagonist demonstrated a dose-dependently attenuation of 2-AG beneficial effects. The results of the aforementioned study showed that 2-AG administration in TBI mice model generated cerebral protection via decreasing neuronal excitotoxicity, inhibiting the production of TNF-α and ROS, and lowering cerebral vasoconstriction (56).

In another study, repeated treatments with a CB_2 receptor agonist on BBB integrity, neuronal degeneration, and the behavioral outcome were performed on a murine model of TBI (57). Cannabinoid agonist significantly decreased BBB permeability (indicated by a reduction in sodium fluorescein uptake) and reduced the number of degenerating neurons, compared to the vehicle-treated group. In addition, the improvement was observed in animals treated with cannabinoid agonist on Rota-rod and open field test, which was associated with a prolonged reduction in macrophage/microglia cell counts.

Taken together, cannabinoid agonist treatment after the brain injury attenuated BBB disruption and neuronal degeneration and induced prolonged protective effects on behavior and macrophage/ microglia cell response. Another study examined the acute effects of CB_2 modulation on behavioral deficits, cerebral edema, perivascular substance P, and macrophage/microglial activation in a murine model of TBI (58). After using cortical contusion injury (CCI) surgery to induce TBI or sham surgery, animals received vehicle or 0-1966 as a CB_2

[DOI: 10.32592/Jsurgery.2019.7.1.101]

receptor agonist at 1 and 24h after the injury.

Rota-rod, forelimb cylinder, and open field tests were performed before and 48 h after sham or CCI surgery. The mice who received 0-1966 showed significantly improved locomotor performance and exploratory behavior, compared to vehicle-treated mice. Furthermore, the mice treated with CB_2 receptor antagonist demonstrated a significant decrease in the cerebral edema, number of perivascular areas of substance-P immune-reactivity, and number of activated macrophages/microglial cells in the brains, compared to vehicle-treated mice.

Altogether, selective CB_2 activation showed neuroprotective effects on brain injury. The TBI patients often suffer from cognitive deficits after the incident, and currently, no effective and definite treatment is available. Some of the pathophysiological mechanisms linked to post-TBI cognitive deficits are excitotoxicity, neuroinflammation, and neuro-metabolic dysfunctions with an associated increase in ROS (59).

In one experiment, the effects of CB_1 receptor agonist was investigated on learning and memory-dependent behaviors after an experimental TBI in rats (60). The treatment with CB_1 receptor agonist and arachidonyl-2′-chloroethylamide (1 mg/kg, daily, intraperitoneal) showed to protect and rescue deficits in learning and memory abilities. The CB_2 are expressed at low levels in the brain and have higher concentrations in microglia than neurons; therefore, they are nonpsychotropic in contrast to CB_1 (52-54).

The increased expression of CB_2 are observed in activated microglia (41, 61-65), and therefore, the drugs that act on CB_2 can be selectively used to target microglia for therapeutic purposes. The CB_2 receptor inverse agonists stabilize CB_2 in an inactive state that ultimately activates microglia from M1 state to M2 state. Microglia activation exists in two stages, including 1) M1 state associated with the production of ROS and pro-inflammatory cytokines, as well as 2) M2 state anti-inflammatory and associated with wound healing and debris clearance (66).

In the setting of TBI, activation of CB_2 leads to M1 microglial activation that can be harmful to the recovery process and increases the secondary damage. Braun et al. (67) used a selective CB_2 receptor agonist (i.e., GP1a) and CB_2 receptor antagonist (i.e., AM630) in a murine model of TBI to study the effects of activation of CB_2 in neuroinflammation and neurovascular injury. The GP1a administration (1–5 mg/kg) attenuated pro-inflammatory M1 macrophage polarization, increased anti-inflammatory M2 polarization, reduced edema development, enhanced cerebral blood flow, and improved neurobehavioral outcomes.

On the other hand, CB_2 receptor antagonist worsened the outcomes after TBI. The results showed that CB_2 modulation had a critical role in peripheral immune cells in recovery from TBI, improved motor functions and neurological outcomes, and reduced anxiety after experimental TBI. In another study performed by Anton Reiner et al. (68), daily treatment with a CB_2 receptor inverse agonist (i.e., SMM-189), which started two weeks after establishing an animal model of TBI, attenuated the motor, visual, and emotional deficits.

In another experiment, focal blast model was used to create mild TBI in mice. The goal of the aforementioned study was to find whether TBI-induced loss of neurons in brain regions is linked to motor functions and fear control, as well as the administration of SMM-189 can be effective in rescuing neurons and protecting against functional deficits (69). The obtained results of the study showed that fearfulness after mild TBI might result from the loss of fear-suppressing neuron types in the basolateral amygdala (BLA), and SMM-189 yielded 50-60% rescue of Thy1+ and PARV neuron loss in the BLA. Therefore, SMM-189 may reduce fearfulness after mild TBI.

Overall, SMM-189 rescued damaged neurons and alleviated functional deficits that resulted from TBI, and these actions were induced by selectively modulating microglia to the beneficial M2 state. Cognitive and emotional deficits associated with mild TBI underline the involvement of medial prefrontal cortex (mPFC) and the hippocampus. It should be noted that these two structures are of central importance for cognitive and emotional functions (70-72). Oscillatory neurons activity in specific frequencies synchronize the activity of neurons within and between the structures of mPFC, as well as hippocampus, and this transient synchronization plays a role in cognitive and emotional processes (73-81).

In a study carried out by Yu Liu et al. (82), multi-site multi-electrode detectors were connected to awake and head-fixed mice to record oscillatory neuronal activity in local field potentials to determine if the functioning of these regions was abnormal after mild TBI in an experimental model and administration of a CB_2 receptor inverse agonist (i.e., SMM-189). Significant abnormalities in oscillatory neuronal activity patterns in the CA_1 of hippocampus and mPFC were observed after mild TBI.

The SMM-189 mitigated functional deficits and neuronal injury and reversed most of the observed

[DOI: 10.32592/Jsurgery.2019.7.1.101]

neurophysiological abnormalities. These changes by SMM-189 are thought to be a result of biasing microglia from the pro-inflammatory M1 state to the prohealing M2 state. Mild and severe TBI can result in two and seven times higher relative risk of developing posttraumatic epilepsy (PTE) in suffering individuals than their healthy counterparts, respectively (83).

Endocannabinoids have been studied for their anticonvulsant properties (84). In a study conducted by Xiu Wang et al. (85), after establishing the TBI model in rats, they were monitored for 12 months for the development of PTE. After behavioral monitoring of PTE and nonPTE rats and comparing the changes between two groups, it was observed that the expression of CB_1 and its ligand synthetase (i.e., 2-AG) in the PTE group were significantly higher than those in the nonPTE group 12 month after TBI. These findings suggest that the ECS may have a vital role in the development of PTE after TBI, and the modulation of this system can be a therapeutic option.

Another study has investigated the effects of CB_2 in the actions of Leptin. Mice received an antagonist of CB_2 (i.e., AM630) or the vehicle, then the weight-drop model was used to induce TBI, and after that they received Leptin or vehicle treatment. Leptin alleviated TBI-induced neurological deficits and recovered the expression of cannabinoid receptors, axonal injury markers, and neuroinflammatory components. All these effects generated by Leptin were prevented or decreased when it was administrated in combination with AM630. These results suggested that CB_2 activity has an important role in TBI pathophysiology and recovery (86).

Minocycline, as a highly lipophilic derivative of the antibiotic tetracycline, can suppress microglial activation, reduce cerebral edema, as well as lesion volume, and induce persistent neuroprotection in experimental TBI models (87-91). Minocycline-mediated neuroprotection mechanism has been proposed to be related to the inhibition of microglial activation (92), reduction of activation of the p38 mitogen-activated protein kinase (93), or the attenuation of pro-inflammatory cytokines (94).

To investigate the ECS relation with neuroprotection effects of minocycline, Lopez-Rodriguez et al. (95) studied the involvement of CB_1 and CB_2 in the effects of minocycline on edema and neurological impairment in a mouse-TBI model. Selective CB_1 and CB2 receptor antagonists (i.e., AM251 and AM630, respectively) were administrated to the animals who received minocycline. The results showed that the protective actions of minocycline were all prevented by both CB_1 and CB_2 receptor antagonists suggesting that the activation of cannabinoid receptors are required for the neuroprotective effects of minocycline. Moreover, the activation of these receptors can induce protective effects on the nervous system after injury.

Clinical Studies

In a clinical trial, patients with severe TBI were treated with a dual CB_1/CB_2 receptor agonist (i.e., KN38-7271) to investigate its effects on cerebral injury and its outcome (96). A total of 97 patients received KN38-7271 (1000 and 500 μg) or placebo within 4.5 h after the injury. Then, ICP and cerebral perfusion pressure (CPP) were analyzed from the start of treatment to the end of the 7th day. In addition, the pharmacokinetic efficacy of the drug was measured by survival and neurological improvement or deterioration on the 7th, 14th, 1st, and 3rd days, as well as 6 months after the injury.

The results showed that survival rates were significantly higher in the treatment group within 1 month after the injury, although this effect was not present after 6 months. Furthermore, critical ICP and CPP were less severe and less frequent in treated patients. No severe adverse effects were observed in the patients probably due to CB_1/CB_2 receptor agonists. These findings revealed that KN38-7271 was safe and well-tolerated, improved early survival rates, and induced beneficial effects on ICP and CPP.

In a retrospective review of registered data, adult patients with TBI were investigated for toxicology screen for THC. Moreover, the relationship between the mortality rate after TBI and THC positive screen test was studied (97). The results showed that the mortality rate in the positive THC screen group was significantly decreased, compared to that in the negative THC screen group. After adjusting for differences between the study cohorts on logistic regression, it was observed that a positive THC screen was independently associated with a higher survival rate after TBI. Therefore, it was concluded that a positive THC screen is associated with a decreased mortality rate in adult patients suffering from TBI.

Dexanabinol

Preclinical Studies

The HU-211 is a synthetic nonpsychotropic cannabinoid (45) that act as a noncompetitive NMDA receptor antagonist (46) and have antioxidant (47), as well as anti-inflammatory properties (TNF-α blocking) (48, 98). The HU-211 has been used in preclinical studies in several

[DOI: 10.32592/Jsurgery.2019.7.1.101]

cases. Shohami et al. (99) used HU-211 (25 mg/kg i.p.) in experimental TBI in rats. It was administrated immediately and 1, 2, or 3 h after the injury and the rats were evaluated 1, 24, and 48 h after TBI.

The administration of HU-211 1 and 2 h after the injury was shown to be very effective in improving motor function recovery, reducing BBB breakdown by more than fourfold, and attenuating cerebral edema. However, administration 3 h after the injury was less pronounced. In another study, HU-211 administration (5 mg/kg i.v) in a rat model of TBI, 4 or 6 h after the injury made a significant improvement in neurological severity score (NSS) (100). To evaluate the long-term effects of the drug, the administration was performed 1 h after the injury, and additional doses were given later. The evaluation of NSS for 30 days showed that a single dose of HU-211 given 1 h after the injury or repeated doses during this period improved the clinical outcome.

Furthermore, HU-211 treatment 1 h after the injury was shown to alleviate the impaired cognitive functions in rats based on their performance in the Morris water maze. These results indicated that a therapeutic window of 4 h for HU-211 after the brain injury even with a single dose results in ameliorating the impairment in both motor and cognitive functions. Cytokines are the members of endogenous proteins, which are released by the cells of the immune system and affect the function of local and distant cells.

Interleukin-1 (IL-1), IL-6, and TNF-α have been identified in the brain in several pathological conditions, including various neurological diseases. In a study carried out by Shohami et al. (98), an experimental brain injury model was applied, and the induction of IL-1x, IL-1b, TNF-α, and IL-6 gene mRNA transcription, as well as TNF-α and IL-6 activity, was performed to investigate the effects of HU-211 on TNF-α activity and neuronal protection. The results showed that HU-211 significantly inhibited TNF-α production at a posttranscriptional stage and improved the outcome of brain injury. As initial insult in TBI is followed by the secondary degeneration and failure of the CNS, damage to the optic nerve can lead to the axonal degeneration followed by a loss of retinal ganglion cells.

In a study conducted by M. Zalish et al. (101), long-term effects of HU-211 were investigated on the calibrated crush injury of the rat optic nerve. Treatment with a single intraperitoneal injection of HU-211 (7 mg/kg) began immediately after the injury. Transmission electron microscopic analysis of the excised optic nerves 30 days after the treatment showed that in HU-211 treated rats, the site of injury was traversed by unmyelinated and thinly myelinated axons that could be indicative of regenerative growth. Viable axons were detected in more than three-quarter of HU-211 treated rats. These results revealed that HU-211 was able to prevent the secondary degeneration and promote the generation after the injury to CNS.

Clinical studies

In a phase 1 trial, rising doses of HU-211 were safe and well-tolerated in healthy volunteers (102). In a phase 2 study performed by Knoller et al. (103), HU-211 was used in patients with severe brain injury to study the effects. Drug administration was started within 6 h after the injury, and the clinical outcomes were assessed throughout a 6-month follow-up period. It was observed that HU-211 treatment was safe and well-tolerated in severe head injury and resulted in a significantly better intracranial/cerebral perfusion pressure control without jeopardizing blood pressure. Finally, in a phase 3 study, clinical trial HU-211 was safe with no side effects and not associated with hepatic, renal, or cardiac toxicity. However, the findings showed no indication of differential treatment effects on the control of intracranial pressure or quality of life between HU-211 and placebo in patients (104).

Discussion and Conclusion

The ECS possesses promising effects in the treatment of diverse TBI pathology through releasing endogenous ligands or changes in cannabinoid receptors activity. The roles that ECS play in TBI pathology are as follows: A) Characterizing ligands that target cannabinoid receptors, and B) Regulating the levels of enzymes and making changes in cannabinoid receptors as a consequence of TBI. As it was shown in some studies, the early activation of ECS resulted in better protective effects than late activation. Furthermore, the activation of CB_1 and CB_2 protected locomotor activity and cognitive function in preclinical studies.

The CB_2 activation ameliorates inflammation and modulates immune system towards anti-inflammatory and healing state. The 2-AG showed to decrease inflammation, oxidation, and neuronal cell death via CB_1 mediation. Some known neuroprotective agents, such as Leptin and minocycline, were shown that their protective effects were mediated by CB_1 and CB_2 activity. On the other hand, in clinical studies the activation of

[DOI: 10.32592/Jsurgery.2019.7.1.101]

CB_1 and CB_2 resulted in improved early survival but not late survival. Moreover, some beneficial effects on ICP and CCP were observed in clinical studies. Finally, HU-211 was shown to be effective in decreasing inflammation and protect the motor and cognitive functions in preclinical studies. However, in clinical studies, HU-211 only revealed to be safe and well-tolerated.

One of the main limitations of the present review was no full access to the literature, and due to the inadequacy of abstracts, some studies were forcibly excluded. This problem may affect this narrative review in a harmful way that was not intended by the authors. There are many aspects of ECS that have not been examined. Clinical trials that studied ECS drugs were very limited and showed no statistically significant protective effect in TBI patients, except for a retrospective study that demonstrated a positive screen test for cannabinoid use in TBI patients associated with lower mortality rate. Nonetheless, these data cannot be replicated in a controlled setting. To date, HU-211 is the only cannabinoid that has been used in patients suffering from TBI; however, it could not produce long-term effects in clinical trials.

In conclusion, numerous preclinical studies suggest that the ECS has many targets for therapeutic agents that might help decrease TBI pathologic influences. However, further studies should be performed to thoroughly investigate these targets. Clinical trials still lack the proof for proven evidence in preclinical studies. Therefore, future studies as clinical trials should use a higher number of research subjects and explore more modifications of ECS targets to provide a better target for novel therapeutic agents.

Conflict of Interest

There is no conflict of interests to be declared.

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