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Review

Molecular and Genetic Mechanisms of Traumatic Brain Injury: The Endocannabinoid System as a Modulatory Axis

Hilal Kalkan * and Nicolas Flamand *

Centre de Recherche de l'Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ), Département de Médecine, Faculté de Médecine, Université Laval, Quebec, QC G1V 0A6, Canada
* Correspondence: hilal.kalkan@criucpq.ulaval.ca (H.K.); nicolas.flamand@criucpq.ulaval.ca (N.F.)

Abstract

Traumatic brain injury (TBI) ranks among the top causes of illness and death on a global scale, characterized by a range of complex and diverse pathophysiological processes that include mechanical disruption, excitotoxicity, oxidative stress, and neuroinflammation. At the molecular level, TBI triggers primary and secondary injury mechanisms that affect neuronal survival, synaptic integrity, and long-term neurological outcomes. The endocannabinoid system (ECS), a lipid-based neuromodulatory framework, is a vital regulator of neural homeostasis, synaptic plasticity, and immune responses. This brief review integrates molecular and mechanistic insights into TBI, positioning the ECS as an injury-responsive modulator of neuroinflammation and neurodegeneration. Collectively, these insights position the ECS as a context-dependent modulatory system with therapeutic relevance in TBI.

Keywords: traumatic brain injury; endocannabinoid system; neuroinflammation; excitotoxicity; neuronal cell death

1. Introduction

Traumatic brain injury (TBI) constitutes one of the most prevalent and challenging neurological disorders worldwide, affecting millions of people every year and significantly contributing to long-term disability, mortality, and economic burden [1]. Epidemiological studies suggest that around 0.5 to 1 million patients are admitted to hospitals annually for TBI in the United Kingdom, where it is the primary cause of disability for those under the age of 40 and severely impacts 150 to 200 individuals per million each year [2]. In the United States, over 1.4 million people are affected by TBI every year, and the estimated economic impact surpasses $50 billion [3]. Likewise, in Canada, TBI is a significant public health issue, with hundreds of thousands of cases reported each year, incurring substantial healthcare and societal expenses related to emergency care, rehabilitation, and long-term disability [4]. These statistics likely underrepresent the actual burden since many mild injuries go unreported. Despite considerable progress in understanding the biological mechanisms underlying TBI, a notable gap persists between mechanistic knowledge and the development of effective clinical treatments, underscoring a pressing unmet need [5].

In addition to its immediate neurological impacts, TBI is increasingly acknowledged as a condition that can lead to long-term and often progressive consequences, such as cognitive impairments, behavioral issues, and an increased risk of neurodegenerative diseases [6]. Even mild TBI can be associated with persistent functional limitations. In the TRACK-TBI cohort of patients presenting to U.S. level I trauma centers, 53% of participants with mild TBI reported injury-related functional limitations at 12 months [7]. A significant challenge

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in TBI research and treatment is the condition's pronounced variability [5]. The severity of injuries can vary from mild concussions to severe structural damage; however, clinical outcomes do not always align with initial evaluations. Growing evidence suggests that TBI is characterized not only by mechanical damage but also by intricate interactions between injury-induced molecular pathways and individual-specific factors such as age, pre-existing conditions, and genetic predispositions [8]. This variability complicates understanding mechanisms and developing treatments, as patients with apparently similar injuries may experience markedly different patterns of recovery or deterioration.

At the molecular level, TBI is best viewed as a progressive process that begins with a primary mechanical insult and is perpetuated by a complex array of secondary injury mechanisms [9]. These mechanisms include excitotoxicity from excessive glutamate release, mitochondrial dysfunction and metabolic failure, oxidative stress, neuroinflammation, and disruption of the blood–brain barrier (BBB) [10]. Experimental evidence links persistent neuroinflammation with progressive tissue damage during TBI. In mice, microglial activation persisted for up to one year after injury and was associated with progressive lesion expansion, hippocampal neurodegeneration, and myelin loss [11]. Additionally, TBI affects more than the CNS, initiating systemic responses such as peripheral immune activation, metabolic dysregulation, and multi-organ interactions, thereby framing brain injury as a broad-spectrum systemic disorder [12].

Inherited genetic variation may contribute to differences in outcomes during TBI. For example, Waters et al. (2013) reported an association between the *TNF* promoter polymorphism rs1800629 and unfavorable outcomes six months after injury [13]. This finding suggests that host genetic factors may contribute to recovery, but it does not establish the mechanisms underlying the association [13]. These results support the notion that TBI outcomes stem not only from the injury's characteristics but also from inherent biological factors that influence the host's response.

Within this intricate framework, lipid-mediated signaling pathways have attracted growing interest as key regulators of neurobiological responses [14,15]. Notably, the ECS has emerged as a vital neuromodulatory system at the crossroads of synaptic communication, immune regulation, and metabolic control [16]. This review examines the molecular and genetic mechanisms underlying TBI, emphasizing the interplay between lipid signaling pathways and neuroimmune interactions. Here, we propose the ECS as a central regulatory system that influences the balance between injury progression and repair. Building on previous reviews of cannabinoid signaling and therapeutic approaches in TBI, including those by Schurman and Lichtman and Lins et al. [17,18], the present review broadens this framework by integrating receptor signaling and endocannabinoid metabolism with ECS-related genetic variability, sex-dependent regulation, peripheral and systemic responses, human endocannabinoid alterations, and recent clinical evidence. This framework emphasizes the context-dependent nature of ECS signaling and biological factors that may contribute to interindividual variability in TBI outcome and therapeutic response.

2. The ECS in the CNS and Brain Injury

The ECS encompasses endogenous lipid ligands, collectively known as endocannabinoids (eCBs), primarily anandamide (AEA) and 2-arachidonoylglycerol (2-AG), along with their synthesizing and degrading enzymes, and two primary cannabinoid receptors, CB_1R and CB_2R [19]. Both CB_1R and CB_2R are G protein-coupled receptors (GPCRs) that inhibit voltage-gated N-type and P/Q-type Ca^{2+} channels upon activation [20,21]. In the CNS, CB_1R is found on neurons at presynaptic terminals and on astrocytes, whereas CB_2R is located on microglia, the brain's resident immune cells derived from embryonic yolk-sac progenitors [22,23]. In addition to the two principal CB_1R and CB_2R, the ECS extends

beyond them to include additional receptors, with ongoing research revealing their extent and significance. Among these additional receptors, the most noteworthy include transient receptor potential vanilloid-1 (TRPV1), various GPRs (GPR55 and GPR18), peroxisome proliferator-activated receptor-γ (PPARγ), serotonin receptor 5-HT_{1A}, and adenosine receptor A_{2A} [19,24]. Of these, TRPV1 and PPARγ are of particular interest in the context of TBI, as TRPV1 is known to play a role in pain management and PPARγ is involved in inflammation and neurodegeneration [18]. In contrast to traditional neurotransmitter systems, eCBs are produced "on demand" in response to cellular activity and stress, allowing rapid, localized adjustments in neuronal and immune functions [25].

Functionally, CB_1Rs are mainly found in neurons and modulate synaptic transmission by regulating neurotransmitter release, whereas CB_2Rs are predominantly expressed in immune cells and are significantly upregulated during inflammation and tissue injury. This inducible expression profile positions the CB_2R as a crucial player in neuroimmune interactions, particularly under pathological conditions such as TBI [19,26]. Emerging research shows that ECS signaling is activated in response to excitotoxicity, oxidative stress, and inflammatory triggers, potentially serving as an intrinsic protective mechanism to restore balance [27].

Despite these advancements, the exact role of the ECS in TBI remains partially unclear. Clinical trials illustrate the challenges of translating cannabinoid-related interventions into sustained benefits during TBI. A phase III trial of dexanabinol did not demonstrate improved six-month outcomes [28], while an exploratory trial of the CB_1R/CB_2R agonist KN38-7271 reported an early survival benefit that was not maintained at six months [29]. Moreover, the interaction among ECS signaling, genetic variability, and systemic responses remains largely unexplored, with substantial implications for understanding differences in injury progression and recovery between individuals.

2.1. Cannabinoids and Related Compounds

In addition to the naturally occurring endocannabinoids AEA and 2-AG in the mammalian nervous system, exogenous compounds also modulate ECS signaling [30]. These substances, collectively known as cannabinoids, fall into three categories: endogenous cannabinoids (eCBs), those from the *Cannabis* plant (phytocannabinoids), and artificially created variants (synthetic cannabinoids) [31]. Table 1 summarizes these cannabinoid classes and their functional roles in TBI pathophysiology, along with detailed experimental parameters, including dosing and routes of administration. Together, these studies illustrate that pharmacological or genetic enhancement of endocannabinoid signaling can attenuate selected pathological and functional consequences of TBI in experimental models.

Synthetic cannabinoids represent a pharmacologically heterogeneous group of compounds that should be distinguished from both phytocannabinoids and synthetic inhibitors of endocannabinoid metabolism [32]. Many synthetic cannabinoids were originally developed as experimental tools to characterize CB_1R and CB_2R signaling and include receptor agonists, antagonists, inverse agonists, and ligands with differing receptor selectivity and signaling efficacy [32,33]. In the context of TBI, researchers have used synthetic pharmacological agents to interrogate cannabinoid-dependent mechanisms and therapeutic potential, including direct cannabinoid receptor ligands and compounds that indirectly enhance endocannabinoid signaling by inhibiting FAAH, MAGL, or other metabolic enzymes. Importantly, these experimental and therapeutic approaches should be distinguished from synthetic cannabinoid receptor agonists (SCRAs) used recreationally, sometimes referred to as "designer cannabinoids" [34]. Compared with the partial agonist Δ^9-THC, several SCRAs display substantially greater efficacy at cannabinoid receptors [34,35]. Recreational SCRA exposure has also been associated with severe neurological and cardiovascular toxicity,

including seizures and tachyarrhythmias [36,37]. Consequently, adverse effects associated with recreational synthetic cannabinoids should not be extrapolated directly to controlled pharmacological modulation of the ECS. Conversely, their pharmacological properties illustrate that the biological consequences of cannabinoid receptor activation depend strongly on ligand efficacy, receptor selectivity, and dose [38]. Within TBI research, controlled synthetic ligands and ECS-modulating compounds have therefore been valuable primarily as mechanistic and experimental therapeutic tools, whereas current evidence concerning recreational SCRAs relates predominantly to toxicity rather than therapeutic benefit [17]. Specific synthetic interventions investigated in experimental and clinical TBI, including receptor-directed compounds and inhibitors of endocannabinoid metabolism, are discussed in subsequent sections.

Table 1. Modulation of endocannabinoid signaling in experimental models of traumatic brain injury. Abbreviations: 2-AG, 2-arachidonoylglycerol; CCI, controlled cortical impact; GABA, γ-aminobutyric acid (as in GABAergic); i.p., intraperitoneal; i.v., intravenous; MAGL, monoacylglycerol lipase; Mgll, mouse monoglyceride lipase gene; TBI, traumatic brain injury.

Approach	Compound-Strategy	Dose and Administration	Timing-Regimen	TBI Model	Observed Effects	Refs.
Endocannabinoid supplementation	2-AG	0.1–10 mg/kg, i.v.	Single administration shortly after injury (~15 min)	Closed-head weight-drop TBI	Reduced brain edema and lesion volume; decreased neuronal loss (notably in hippocampus); improved functional recovery	[39]
Pharmacological enhancement of 2-AG	MAGL inhibitor (MJN110)	0.5–2.5 mg/kg, i.p.	Administered 30 min after each of three impacts, followed by once-daily dosing for five additional days (eight injections in total).	Repetitive closed-head injury (CCI-based paradigm)	Attenuated neuroinflammation; reduced cell death; restored glutamatergic and GABAergic receptor balance; improved cognitive and locomotor performance	[40]
Genetic enhancement of endocannabinoid signaling	Astrocyte-specific MAGL deletion	-	Constitutive (genetic model)	Repetitive closed-head injury (CCI paradigm)	Decreased neuroinflammatory responses; limited injury-induced transcriptional alterations; reduced neurodegeneration; preserved cognitive function	[41]

2.2. Phytocannabinoids

Phytocannabinoids are naturally occurring compounds extracted from the *Cannabis sativa* plant that exhibit biological activity within the ECS [42]. The main phytocannabinoids include Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [43]. THC is the most recognized phytocannabinoid and the primary psychoactive element of the *Cannabis* plant [42]. THC's pharmacological effects mimic those of the eCB AEA, functioning as a partial agonist at CB_1R and CB_2R [44]. Additionally, like AEA, THC administration reduces neuronal firing at the presynaptic level [18]. FDA-approved synthetic cannabinoid medicines include dronabinol, a synthetic form of Δ^9-THC, and nabilone, a synthetic THC analog [45]. There is a possibility that THC could help alleviate nausea and vomiting in the context of acute TBI [18]. It has been studied directly in TBI pathology models and indirectly in certain clinical TBI populations, with promising results for therapeutic applications beyond nausea [46–48].

CBD has complex, assay-dependent pharmacology; in cellular assays, it can act as a negative allosteric modulator of CB_1R [49]. CBD can influence AEA availability through mechanisms that depend on the experimental system. Inhibition of fatty acid amide hydrolase (FAAH), the enzyme that breaks down AEA, has been reported in rodent preparations [50], CBD did not inhibit human FAAH in the assays reported by Elmes et al.; interference with intracellular fatty acid-binding proteins provides an alternative mechanism [51]. This is significant for TBI, as in a mouse model of TBI, treatment with the FAAH inhibitor PF-3845 improved fine motor performance, hippocampus-dependent working memory, and anxiety-like behavior [52]. Additionally, CBD directly activates serotonin 5-HT1A receptors, which could impact mood and anxiety [53,54]. It acts as a weak agonist at TRPV1 receptors, potentially modulating pain and synaptic plasticity [55]. As a PPARγ agonist, it may also be connected to neurodegeneration and inflammation [56]. CBD's actions at these receptors could benefit TBI, particularly through PPARγ activation, which reduces neurodegeneration and inflammation [17].

2.3. Injury-Induced ECS Responses and Their Context-Dependent Effects

The ECS has been identified as an essential neuromodulatory network with widespread presence and functional significance across various cell types within the central nervous system, including neurons, astrocytes, microglia, and components of the cerebrovasculature [38]. This extensive distribution underpins its role in a diverse array of physiological and pathological processes, particularly in neural injury.

Recent preclinical research across TBI models highlights the neuroprotective role of eCBs and the ECS in facilitating recovery from TBI. For example, the administration of synthetic 2-AG in a mouse model of closed-head TBI resulted in a significant reduction in edema and infarct size, decreased cell death in the hippocampus, and enhanced functional recovery [39]. These beneficial outcomes appear to be mediated by the CB_1R, suggesting a potential protective role of the ECS following injury. Further supporting evidence is drawn from a study that enhanced the effects of 2-AG by inhibiting its degrading enzyme, monoacylglycerol lipase (MAGL), in a controlled cortical impact (CCI) model. In this study, administration of the MAGL inhibitor MJN110 to CCI mice post-injury led to reduced inflammatory markers, decreased cell death, normalization of altered glutamate and gamma-aminobutyric acid (GABA) receptor levels, and improved cognitive and motor performance [40]. In a repeated mild TBI (mTBI) mouse model, deletion of astrocyte-specific MAGL reduced neuroinflammation, attenuated alterations in TBI-induced gene expression, and slowed neurodegenerative changes and cognitive decline. These favorable effects were also mediated by the CB_1R [41]. Additionally, the administration of the FAAH inhibitor URB597 exhibited neuroprotective properties in an oxygen-glucose deprivation injury model, demonstrating antioxidant, anti-inflammatory, and anti-apoptotic effects [57]. Lastly, in a kainic acid-induced excitotoxicity model, AEA levels in the hippocampus increased rapidly, conferring CB_1R-dependent neuroprotection [58]. Collectively, these studies demonstrate that injury-induced ECS signaling can engage protective mechanisms in experimental models; however, the consequences of ECS activation depend on the ligand, receptor, cellular context, metabolic pathway, timing, and magnitude of signaling. Thus, enhancement of endocannabinoid signaling should not be considered uniformly neuroprotective, but rather as a context-dependent response whose therapeutic relevance depends on the specific component of the ECS being targeted.

2.4. Evaluation of Cannabinoid-Based Interventions in Preclinical Models of TBI

Several preclinical investigations have examined the primary phytocannabinoid constituents in TBI models, yielding promising results. In a mouse model of mTBI induced by

weight-drop, the injury resulted in reduced sociability, heightened aggression, and tactile allodynia, observed 14 days post-injury. Notably, these symptoms improved with daily oral administration of 10% CBD oil for either a 14-day period or from days 50 to 60 following the injury. Additionally, the mTBI model showed elevated levels of D-aspartate, glutamate, and GABA in the medial prefrontal cortex, and CBD treatment effectively alleviated these alterations [59].

In a rat model employing weight-drop and craniotomy (modified Feeney's model), CBD (10 mg/kg) was administered 30 min prior to the injury and again six hours afterward. The results indicated that CBD treatment improved BBB integrity by decreasing aquaporin-4 expression and increasing claudin-5 and occludin expression. Direct observation of BBB leakage was conducted using Evans' Blue assay. Furthermore, CBD administration resulted in reduced GFAP expression and lower levels of the pro-inflammatory mediators Tumor necrosis factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β) compared with the control group [60].

In another study involving rats with moderate TBI (using the CCI model), Friedman and colleagues applied various high CBD, low THC botanical formulations directly onto the open skull over the dura mater at the injury site, utilizing a gelfoam matrix immediately following the injury. Additional groups received both the cannabinoid gel foam matrix and systemic administration of CBD ten minutes post-injury, continuing for 14 non-consecutive days thereafter [61]. The combination of gelfoam and systemic administration proved superior to either method alone, resulting in reduced defecation scores (an indicator of anxiety), smaller lesion volumes, lesser loss of hippocampal neurons, diminished neural pathology, and exhibited anti-inflammatory properties, as evidenced by reduced GFAP immunoreactivity alongside concurrent improvements in motor and cognitive functions. In summary, these studies collectively indicate that CBD treatment has multifaceted effects, offering benefits in inflammation, cognition, neurobehavioral deficits, lesion size, and BBB disruption during TBI.

In contrast, data pertaining to THC treatment in TBI models is more complex, with sex and timing emerging as critical factors. In a repeated injury model utilizing weight-drop in rats, THC (1.25 mg/kg, i.p.) was administered in six intermittent pre-injury doses or twelve consecutive post-injury doses. Post-injury THC treatment was associated with an increase in anxiety-like behavior in the elevated plus maze, although it did not influence behavior in the open field task. Interestingly, depression-like behavior assessed in the forced swim task improved in male rats treated with THC post-injury, while female rats displayed a more pronounced depression-like state. Additionally, post-injury THC treatment successfully prevented telomere shortening following repeated mTBI [48].

Consistent with prior studies, the authors observed increased microglial activation following repeated mTBI [62,63]. However, they did not observe any impact of THC treatment on microglial activation in limbic system structures, such as the hippocampus and nucleus accumbens. Instead, THC was found to elevate IBA1 immunoreactivity in the prefrontal cortex, suggesting a lack of therapeutic benefit regarding neuroinflammation in that specific area [46].

Conversely, in a male-only mouse model of CCI for TBI, THC treatment (3 mg/kg, i.p., daily for three days) improved motor function. Differences in dose, species, sex, age, injury model, and treatment schedule may contribute to the differing findings, although these studies do not establish which factors account for them. This improvement in motor performance coincided with elevated levels of brain-derived neurotrophic factor and glial-derived neurotrophic factor, both associated with neuronal and glial repair across various brain regions [47]. Moreover, THC administration was associated with increased levels of 2-AG in the brain, which aligned with improved short-term working memory [48]. These

findings provide grounds for optimism regarding the potential application of THC in the management of TBI.

2.5. Genetic Variability of Endocannabinoid System Components and Implications for TBI

Interindividual variability in TBI outcomes remains a major challenge in neurotrauma research [64]. Patients with apparently comparable injury severity may follow markedly different recovery trajectories, ranging from near-complete functional restoration to persistent cognitive, affective, and neurodegenerative complications [65]. While age, sex, injury mechanism, comorbidities, and treatment timing influence this variability, genetic background is increasingly recognized as an important biological determinant of injury response [66]. In this context, genetic variability within the ECS is particularly relevant because this system regulates several processes central to TBI pathophysiology, including synaptic excitability, glutamate release, neuroinflammation, stress adaptation, BBB integrity, and neuronal survival [67].

Most available genetic evidence does not yet come directly from TBI cohorts, but from related fields such as trauma exposure, post-traumatic stress disorder (PTSD), depression, neuroinflammation, cognition, and neurodegenerative disease. This limitation is important, but it does not reduce the biological relevance of ECS genetics to TBI. Instead, it highlights a key knowledge gap: ECS-related polymorphisms may influence the same molecular pathways that determine secondary injury progression and long-term recovery, yet they remain insufficiently studied in neurotrauma populations. Therefore, integrating evidence from trauma-related and neurobiological studies provides a useful framework for understanding how ECS genetic variability may contribute to TBI heterogeneity.

2.5.1. CNR1 Polymorphisms: Synaptic Regulation, Stress Vulnerability, and Cognitive Outcomes

Among ECS-related genes, *CNR1* has received the greatest attention in studies investigating the relationship between cannabinoid signaling and trauma-related outcomes [68]. Several polymorphisms within *CNR1* have been associated with differences in emotional regulation, cognitive performance, stress responsiveness, and susceptibility to neuropsychiatric disorders. Although direct studies in TBI populations remain limited, these findings suggest that genetic variation in CB1R signaling may contribute to the marked heterogeneity observed in post-traumatic recovery.

Several *CNR1* polymorphisms have been associated with neuropsychiatric and cognitive phenotypes relevant to TBI [69]. The synonymous variant rs1049353 has been examined in relation to depression, emotional processing, antidepressant response, and stress-related phenotypes [70]. Although they do not alter the CB1R amino acid sequence, synonymous variants may still influence mRNA stability, translation efficiency, receptor expression, or their association with other functional variants. Furthermore, among U.S. veterans with histories of childhood abuse, carriers of the *CNR1* rs1049353 A allele reported greater PTSD symptom severity, particularly anxious arousal, than G/G homozygotes [71]. However, not all research supports this finding. One possible explanation for the conflicting results is that previous studies may not have considered the phenotypic variability of PTSD symptoms or the environmental factors that could influence this polymorphism. In the context of TBI, such effects could be important because even subtle changes in CB1R availability may alter the capacity of injured neural circuits to restrain excitotoxic neurotransmission and regulate stress-related signaling.

Another important variant is *CNR1* rs806371 [72]. In a prospective study of trauma-injury survivors, Fitzgerald et al. evaluated circulating endocannabinoids shortly after traumatic injury and again six months later, together with genetic variation in *CNR1*, *FAAH*,

and *MAGL*. The study reported that carriers of the minor allele of *CNR1* rs806371 showed greater depressive symptom severity six months after trauma [73]. Importantly, this association suggests that ECS genetic variability may influence long-term psychological outcomes after injury, potentially through stress-response pathways rather than through injury severity alone. This is highly relevant to TBI, where depression, anxiety, emotional dysregulation, and post-traumatic symptoms are common long-term sequelae.

The *CNR1* rs2180619 polymorphism has also been investigated in stress- and trauma-related contexts [74]. In a cohort of military veterans exposed to deployment-related stress, Leen et al. examined interactions among *FAAH* rs324420, corticotropin-releasing hormone receptor 1 (*CRHR1*) rs110402, and *CNR1* rs2180619 in relation to anxiety and trauma-related symptoms. Although the study did not identify significant direct or interaction effects of these polymorphisms on anxiety or PTSD symptoms, childhood trauma was a significant covariate across models [75]. The study did not establish the tested genetic associations or interactions [75]. Gene–environment interactions remain a plausible hypothesis in TBI research, but these null results do not demonstrate them.

CNR1 genetic variability has also been linked to structural and functional brain phenotypes [74]. In schizophrenia cohorts, *CNR1* variants were associated with white matter volume differences, and interactions between *CNR1* genotype and marijuana misuse were linked to greater white matter deficits and cognitive impairment [76]. Although this study was not performed in TBI patients, the findings are mechanistically relevant because white matter integrity and cognitive function are central determinants of TBI outcome, particularly in diffuse axonal injury. Similarly, Colizzi et al. showed that *CNR1* rs1406977 was associated with prefrontal *CNR1* mRNA expression, and that genotype interacted with cannabis exposure to influence prefrontal connectivity and working memory performance [74]. These findings indicate that *CNR1* polymorphisms can influence functional brain networks involved in executive function, a domain frequently impaired during TBI.

Together, these studies suggest that *CNR1* polymorphisms may influence TBI-relevant outcomes through several converging mechanisms. First, altered CB1R signaling may affect excitotoxic vulnerability by changing the efficiency of eCB-mediated suppression of glutamate release. Second, *CNR1* variants may influence frontolimbic circuitry involved in emotional regulation, stress adaptation, and post-traumatic psychiatric symptoms. Third, genetic effects on white matter integrity and prefrontal connectivity may contribute to variability in cognitive recovery. However, direct studies examining *CNR1* polymorphisms in well-characterized TBI cohorts remain limited. Therefore, while the available evidence strongly supports biological plausibility, future research must determine whether *CNR1* variants predict acute injury severity, secondary injury biomarkers, neuroimaging outcomes, or long-term cognitive and psychiatric recovery during TBI.

2.5.2. FAAH Polymorphisms: Anandamide Signaling, Stress Responsiveness, and Recovery After Trauma

Among eCB-metabolizing enzymes, FAAH is one of the most genetically and functionally characterized. FAAH encodes the major intracellular serine hydrolase responsible for AEA degradation, thereby regulating the magnitude and duration of AEA-mediated signaling. Because AEA regulates emotional processing, stress responsiveness, neuroinflammation, and synaptic homeostasis, genetic variation that modifies FAAH expression or enzymatic activity may influence several biological responses relevant to TBI [77].

The most extensively studied *FAAH* variant is rs324420, also referred to as C385A, a single-nucleotide polymorphism that results in a proline-to-threonine substitution at amino acid 129 (P129T) [78]. This missense substitution is not merely a neutral genetic marker; functional studies indicate that the A-allele reduces FAAH protein stability and

enzymatic activity [79]. As a result, individuals carrying this variant may exhibit reduced AEA degradation and relatively higher endocannabinoid tone. Mechanistically, this means that *FAAH* genotype can influence how long AEA remains available after cellular activation or stress, thereby shaping downstream CB_1R-dependent and non-CB_1R-dependent signaling pathways.

This genetic effect is particularly relevant in the context of trauma because AEA signaling is closely linked to stress adaptation [80]. Reduced *FAAH* activity may increase AEA availability in brain regions involved in fear processing and emotional regulation, including the amygdala, hippocampus, and prefrontal cortex [81]. Dincheva et al. (2015) found enhanced fear extinction in human carriers of the *FAAH* rs324420 A-allele and in mice carrying the corresponding variant, together with reduced anxiety-like behavior in the mice [78]. These findings support a role for *FAAH* genetic variation in fear regulation, but do not establish its effects on inflammatory responses or recovery during TBI [78].

Several human studies support the idea that *FAAH* genetic variation contributes to trauma-related phenotypes, although its effects appear highly dependent on environmental context. The most extensively investigated *FAAH* variant, rs324420 (C385A), has been associated with reduced FAAH activity and increased AEA availability, thereby prolonging eCB signaling [82]. While elevated AEA levels are often considered beneficial due to their anxiolytic and stress-buffering properties, evidence suggests that the long-term consequences of genetically altered *FAAH* activity may be more complex [83]. In a cohort of 858 individuals, Lazary et al. demonstrated a significant interaction between *FAAH* rs324420 and childhood adversity, whereby carriers of the A-allele exhibited significantly greater anxiety and depressive symptoms following repetitive early-life trauma compared with CC homozygotes. Notably, the polymorphism alone did not predict psychopathology, highlighting the importance of gene–environment interactions in shaping clinical outcomes. Mechanistically, the authors proposed that persistently elevated AEA concentrations during neurodevelopment may induce compensatory downregulation of CB1R signaling, thereby reducing the ECS's ability to restrain glutamatergic transmission and HPA axis activation under chronic stress [84].

Lifelong genetic variation in FAAH should not be assumed to reproduce the effects of short-term pharmacological inhibition. In mice exposed to chronic unpredictable stress, repeated URB597 treatment increased dentate gyrus neural progenitor proliferation and BDNF expression and reduced depressive-like behavior [85]. These model-specific findings do not establish the consequences of lifelong *FAAH* variation during TBI.

These findings are particularly relevant to TBI because HPA axis activation, neuroinflammatory signaling, and impaired neuroplasticity contribute to the progression of secondary injury and long-term neurological dysfunction. Variability in *FAAH* activity may therefore influence not only emotional resilience after trauma but also the magnitude of endogenous neuroprotective responses triggered following brain injury. Although direct studies in TBI populations are lacking, the available evidence suggests that *FAAH* genotype may represent an important modifier of individual susceptibility to stress-related and neuroinflammatory sequelae after neurotrauma.

Pharmacological studies suggest that FAAH activity can influence inflammatory and neuroendocrine responses relevant to TBI. In mice with TBI, the FAAH inhibitor PF-3845 attenuated inflammatory microglial/macrophage responses and improved functional recovery [52]. In a separate rat stress model, administration of the FAAH inhibitor URB597 into the basolateral amygdala reduced stress-induced corticosterone secretion [86]. These findings provide a rationale for investigating FAAH-related mechanisms during TBI, but do not demonstrate that inherited *FAAH* variants produce the same effects.

However, direct evidence linking *FAAH* polymorphisms to neurological outcomes during TBI remains limited. Most available data derive from studies of trauma exposure, depression, anxiety, post-traumatic stress symptoms, and stress-related phenotypes rather than from well-characterized TBI cohorts. Therefore, it remains unknown whether *FAAH* rs324420 or other *FAAH* variants directly influence lesion progression, BBB disruption, neuroinflammatory burden, cognitive recovery, or neurodegenerative risk during TBI. Future studies should integrate *FAAH* genotyping with longitudinal clinical outcomes, neuroimaging, inflammatory biomarkers, and lipidomic measurements of AEA and related mediators. Such approaches would help determine whether *FAAH* genetic variability contributes to patient stratification and whether FAAH-regulated AEA signaling represents a precision therapeutic target in TBI.

2.5.3. CNR2 Polymorphisms: Neuroimmune Regulation and Implications for TBI

Compared with *CNR1*, considerably less is known regarding the contribution of *CNR2* polymorphisms to neurological outcomes during TBI [87]. Nevertheless, accumulating evidence suggests that genetic variation in *CNR2*, which encodes CB_2R, may be particularly relevant to TBI due to its close association with immune regulation and neuroinflammatory signaling [26]. While CB_2R expression is relatively low under physiological conditions, it increases markedly following tissue injury and during neuroinflammatory states, suggesting that genetic factors influencing receptor function may have greater consequences during disease than under basal conditions [19].

Among the reported *CNR2* variants, the best-characterized is the functional Q63R polymorphism (rs35761398), which involves a glutamine-to-arginine substitution at amino acid position 63 within the receptor's intracellular domain [88]. Wang et al. found that activation of both the Q63 and R63 *CB2R* variants induced extracellular signal-regulated kinase (ERK) phosphorylation in immune cells, but the response was weaker for the R63 variant [89]. These findings support an effect of Q63R on this signaling pathway, although its consequences for inflammation and recovery during TBI remain undetermined. The biological implications of this variant extend beyond peripheral immunity. CB_2R is increasingly recognized as a key regulator of microglial activation, cytokine production, leukocyte recruitment, and neuroimmune communication [19]. Experimental studies show that CB_2R activation suppresses the release of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), while promoting inflammation resolution and facilitating tissue repair [90]. Therefore, inherited variation that reduces receptor responsiveness could theoretically shift the balance toward a more sustained inflammatory phenotype following brain injury.

Although direct investigations of *CNR2* polymorphisms in TBI cohorts remain scarce, evidence from other neurological and inflammatory disorders supports the biological relevance of altered CB_2R signaling [91]. The Q63R variant has been associated with several immune-mediated conditions, including autoimmune diseases and chronic inflammatory disorders, suggesting that CB_2R-mediated immunoregulation is sensitive to genetic variation [88,89,92]. Furthermore, increased CB_2R expression has been documented in multiple neurodegenerative and neuroinflammatory conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and HIV-associated neurocognitive disorders [93–97]. Collectively, these observations support the concept that CB_2R functions as an inducible protective pathway activated by chronic neuroinflammatory stress.

Although inflammatory responses can contribute to repair, prolonged activation can exacerbate neuronal damage and contribute to chronic neurodegeneration [11]. Experimental TBI studies support a role for CB_2R in regulating inflammatory and neurovascular responses. In mice, selective CB_2R agonists attenuated post-traumatic inflammation, whereas receptor

blockade or deletion exacerbated aspects of the response [98]. These findings provide a rationale for investigating whether inherited *CNR2* variants influence recovery, but do not establish the effects of human polymorphisms on inflammation or tissue repair during TBI.

Despite these biologically plausible mechanisms, direct evidence linking *CNR2* polymorphisms to TBI susceptibility, lesion progression, cognitive recovery, or long-term neurological outcomes remains limited. This represents an important gap in the current literature, particularly given the strong preclinical evidence supporting CB_2R as a therapeutic target in neurotrauma. Future studies integrating *CNR2* genotyping with inflammatory biomarkers, neuroimaging measures, eCB profiling, and longitudinal clinical outcomes may clarify whether genetic variability in CB_2R signaling contributes to the marked heterogeneity observed among patients with TBI. Such investigations may also help identify patient populations most likely to benefit from therapies targeting CB_2R-dependent neuroimmune pathways.

2.5.4. MAGL Genetic Variation and Regulation of 2-AG Signaling

Among genes involved in eCBs metabolism, MAGL is a particularly relevant candidate for modifying responses to neurological and psychological trauma [99]. MAGL is the principal hydrolytic enzyme responsible for the termination of 2-AG signaling in the brain [100]. Consequently, variation in MAGL expression or activity can influence both the magnitude and duration of 2-AG-mediated signaling and the downstream metabolic fate of this lipid mediator [101]. Unlike *FAAH*, for which the functional consequences of rs324420 are relatively well characterized, the human genetic literature on MAGL remains limited, and the functional effects of commonly investigated *MAGL* polymorphisms have not been fully resolved.

The most extensively studied *MAGL* polymorphism is rs604300, an intronic variant primarily studied in relation to stress exposure and behavioral phenotypes. Carey et al. examined genetic variability across several endocannabinoid-related genes in the context of childhood sexual abuse and cannabis dependence. At the gene level, *MAGL* significantly interacted with childhood adversity, and rs604300 accounted for the strongest individual single-nucleotide polymorphism (SNP) effect. They observed the interaction in an initial sample and replicated it in an independent cohort. Importantly, carriers of the minor A-allele showed relative protection from the increase in cannabis-dependence symptoms associated with childhood adversity. Thus, the effect of rs604300 was not evident as a simple main genetic effect but emerged in the presence of an environmental stressor, supporting a gene-environment model of *MAGL*-related vulnerability [102].

The investigators subsequently examined a neurobiological phenotype that could potentially explain this association. In an independent neuroimaging cohort, rs604300 interacted with early-life adversity to predict basolateral amygdala habituation to repeated threat-related stimuli. A-allele carriers exposed to greater adversity exhibited stronger amygdala habituation, reflecting a greater reduction in threat responsivity over repeated exposure. Because impaired habituation of amygdala responses is associated with persistent stress sensitivity, these findings suggested that *MAGL*-related variation may influence neural adaptation to stressful experiences [102]. The authors further proposed that rs604300 could be associated with epigenetic modulation of MAGL expression, although the molecular mechanism linking this intronic variant to enzyme expression or activity remains unresolved. Therefore, rs604300 should currently be regarded as a regulatory candidate rather than as a functionally established *MAGL* variant.

These observations are relevant to TBI because 2-AG signaling is strongly recruited following neural injury and stress [99]. Changes in *MAGL* activity could theoretically modify the duration of this response by determining how quickly 2-AG is hydrolyzed.

However, the biological consequences of altered *MAGL* activity are more complex than simply increasing or decreasing cannabinoid receptor signaling. Hydrolysis of 2-AG by MAGL produces arachidonic acid, which can subsequently enter cyclooxygenase- and lipoxygenase-dependent pathways to generate prostaglandins and other inflammatory lipid mediators [103]. MAGL therefore sits at a metabolic intersection between endocannabinoid signaling and eicosanoid production [103]. Increased *MAGL* activity could reduce available 2-AG while simultaneously increasing the substrate pool for inflammatory mediator synthesis, whereas reduced *MAGL* activity may prolong 2-AG signaling while limiting arachidonic acid-derived inflammatory products [100].

Preclinical findings strongly support the importance of this metabolic balance in brain injury. In mouse brain preparations, MAGL accounted for approximately 85% of measured 2-AG hydrolysis [104]. In models of neuroinflammation, neurodegeneration, ischemic injury, and TBI, MAGL inhibition has been associated with attenuated inflammatory signaling, preserved synaptic function, and improved neurological outcomes [40,105,106]. Experimental TBI studies have further shown that augmenting 2-AG signaling through MAGL inhibition can reduce inflammatory markers and neuronal loss and improve cognitive or locomotor recovery [107–112]. These findings establish MAGL as a biologically relevant regulator of pathways that contribute to secondary brain injury, even though they do not themselves demonstrate a genetic effect in human TBI.

An important counterpoint is that sustained MAGL suppression is not necessarily beneficial. Chronic, near-complete inhibition of MAGL produces pronounced elevations in brain 2-AG and can lead to CB1R desensitization and functional antagonism of the ECS [106]. This observation indicates that *MAGL* activity should be considered part of a dynamic regulatory system rather than a simple protective-harmful continuum.

Human trauma data further illustrate this complexity. Fitzgerald et al. measured circulating 2-AG and AEA after traumatic injury and again six months later while also examining variants in *CNR1*, *FAAH*, and *MAGL*. Higher serum 2-AG concentrations shortly after injury predicted greater depressive symptom severity six months later. In contrast, *MAGL* rs604300 itself was not identified as a significant predictor of depression severity; the significant genetic association in that study involved *CNR1* rs806371 [73]. These findings matter because they argue against assuming that increased 2-AG is uniformly neuroprotective in humans. Acute elevation of circulating 2-AG may instead reflect the magnitude of the biological stress response, compensatory ECS recruitment, altered 2-AG degradation, or a combination of these mechanisms.

Taken together, current evidence identifies *MAGL* as a compelling but incompletely characterized genetic candidate in trauma biology. The rs604300 findings indicate that *MAGL* variation can interact with early-life adversity and influence stress-related behavioral and neural phenotypes [102], while experimental evidence shows that *MAGL* activity directly regulates molecular pathways highly relevant to TBI, including eCB tone, inflammatory lipid production, synaptic signaling, and neuroinflammation [27,40,110]. However, no convincing evidence currently shows that rs604300 or another common *MAGL* polymorphism directly predicts TBI susceptibility or neurological recovery. Future studies should therefore move beyond genotype–phenotype association alone and combine *MAGL* genotyping with measurements of MAGL expression or activity, circulating and central 2-AG concentrations, lipidomic profiles of arachidonic acid-derived mediators, neuroimaging, and longitudinal neurological outcomes. Such studies will be necessary to determine whether *MAGL* variation constitutes a true modifier of post-TBI biology or primarily influences broader stress-related phenotypes.

Collectively, the available evidence indicates that genetic variation within the ECS can modify endocannabinoid tone, receptor responsiveness, stress-related neural circuitry, and

immune regulation. However, an important distinction emerges between biological plausibility and direct evidence in TBI. Functional consequences are relatively well characterized for variants such as *FAAH* rs324420 and *CNR2* rs35761398, whereas *CNR1* and *MAGL* variants have predominantly been associated with stress-related, psychiatric, or neuroimaging phenotypes rather than neurological recovery during TBI. Large, prospective TBI cohorts integrating ECS genotyping with circulating or cerebrospinal fluid (CSF) endocannabinoid profiles, inflammatory biomarkers, neuroimaging, and longitudinal neurological outcomes are currently lacking. Thus, ECS genetic variability may contribute to interindividual heterogeneity during TBI, but its prognostic value and therapeutic implications remain unclear.

2.5.5. Sex-Dependent Regulation of the ECS in TBI

Sex is an increasingly recognized biological variable in TBI research, yet mechanistic studies of the ECS have rarely integrated it [66]. Epidemiological and clinical data indicate that TBI incidence, injury mechanisms, and recovery trajectories differ between men and women. In the TRACK-TBI cohort, women with mTBI reported greater persistent cognitive and somatic post-concussion symptoms than men, with somatic symptoms particularly pronounced among women aged 35–49 years; however, hormonal measurements were not performed, preventing direct attribution of these differences to reproductive endocrine status [113]. These differences may reflect a combination of injury biomechanics, gonadal hormone status, immune reactivity, and genetic background, several of which converge on the ECS-regulated pathways described throughout this review, including excitotoxicity, neuroinflammation, and BBB integrity. Several preclinical studies discussed in this review, including investigations of FAAH inhibition with PF-3845 and MAGL inhibition with JZL184, used male mice [52,110]. These studies therefore do not establish whether females show comparable benefits, highlighting the need for direct comparisons of treatment responses between sexes.

Baseline sex differences in the ECS provide a biological rationale for investigating sex-dependent responses to TBI. In uninjured Sprague-Dawley rats, females had higher AEA concentrations in the periaqueductal gray (PAG) and primary visual cortex than males, but lower 2-AG concentrations and a lower 2-AG: AEA ratio specifically in the PAG. Immunohistochemical analyses showed greater CB_1R and MAGL immunoreactivity in females in both the lateral PAG and primary visual cortex, whereas the lateral PAG showed greater CB_2R immunoreactivity and the cortex showed greater ABHD6 (alpha/beta-hydrolase domain-containing 6) immunoreactivity. These findings demonstrate region-specific sex differences in ECS components under baseline conditions [114]. Comparable dimorphism has been reported in humans: positron emission tomography imaging of CB_1R availability shows region-specific differences between men and women [115]. Human serum lipidomic analyses similarly show sex- and age-related variation in ECS-related lipids, with higher overall concentrations of AEA, 2-AG, oleoylethanolamide (OEA), and palmitoylethanolamide (PEA) reported in males, although the magnitude and temporal pattern of these differences vary across the lifespan [116]. CB_1R- and CB_2R-mediated signaling directly shapes glutamate release, microglial activation, and BBB integrity. These basal differences in ECS tone provide a plausible biological basis for sex-dependent vulnerability and pharmacological responsiveness during TBI, although this relationship has not yet been demonstrated directly in humans.

The interaction between gonadal hormones and ECS signaling is particularly relevant to TBI because brain injury itself may alter endocrine function. The failure of large progesterone trials, including ProTECT III and SyNAPSe, despite encouraging preclinical findings further illustrates the difficulty of translating hormone-sensitive neuroprotective mechanisms into heterogeneous TBI populations [117–119]. Whether interindividual differences in ECS

signaling contribute to this variability remains unknown. Moreover, interactions among sex hormones and *CNR1* and *FAAH* genetic variability may represent an additional source of biological heterogeneity, although genotype-by-sex effects remain largely unexplored in TBI populations.

Consistent with this hormone–ECS crosstalk, sex-dependent ECS regulation is also evident in experimental stress models. In rats exposed to repeated immobilization and tail-shock stress, females had higher basal *Cnr1* and *Cnr2* mRNA levels in the amygdala, hippocampus, prefrontal cortex, and hypothalamus than males. Repeated stress reduced *Cnr1* mRNA levels in the hippocampus, hypothalamus, and prefrontal cortex of females, while increasing hypothalamic *Cnr1* mRNA levels in males. Prefrontal CB1R protein levels were also reduced in stressed females [120].

Direct evidence that sex modifies the response to ECS-targeted intervention comes from studies of 2-AG metabolism following repeated mTBI. In male and female rats subjected to repeated mTBI, pharmacological inhibition of MAGL with JZL184 produced sex-dependent behavioral effects. Repeated injury increased subsequent alcohol consumption in females but not males, whereas early anxiety-like behavior was more evident in males. JZL184 did not reverse the increased alcohol consumption observed in injured females and increased anxiety-like behavior in males during the early post-injury period [121]. These findings demonstrate that increasing 2-AG availability through MAGL inhibition does not necessarily produce equivalent outcomes across sexes and that its effects depend on sex, behavioral endpoint, and post-injury timing. As noted in Section 2.4, post-injury THC produced more pronounced depression-like behavior in female rats than in males in a repeated mTBI model [46]. Plasma lipidomic profiling following single and repeated mTBI further revealed a dynamic, sex-dependent endolipid response. At baseline, approximately 31% of measured plasma endolipids differed between sexes, predominantly with higher concentrations in females, whereas the first head injury induced a broader acute lipidomic response in males than females. Several fatty acids involved in inflammatory and pro-resolving lipid pathways also showed sex-dependent responses to injury. Interestingly, AEA did not show significant sex- or injury-dependent changes within the acute sampling intervals, whereas 2-AG was higher in females at baseline and immediately following the first injury. These findings indicate that sex-dependent responses to mTBI extend beyond the canonical eCBs and involve broader lipid networks whose regulation varies by injury number and post-injury timing [122]. However, because these changes were measured in plasma and their functional relationship to neurological recovery was not directly established, it remains unclear whether the observed sex-dependent lipid profiles represent protective, maladaptive, or compensatory responses.

Evidence from trauma-related neurobehavioral models further demonstrates that sex can determine which cellular pathways are recruited by cannabinoid signaling. In a recent study of THC-modulated fear memory, males required coordinated CB_1R and PPARγ signaling acting through microglial recruitment and morphological activation in the hippocampus, whereas females achieved an equivalent behavioral effect through CB_1R signaling alone, independent of microglia and restricted to specific estrous-cycle phases [123]. These findings suggest that similar behavioral responses to cannabinoids can involve different mechanisms in males and females. Whether these differences influence responses to ECS-targeted treatments during TBI requires direct investigation in TBI models.

Importantly, the available evidence does not support categorizing either male or female ECS signaling as uniformly more neuroprotective; rather, the direction and magnitude of sex effects vary according to age, hormonal state, brain region, injury paradigm, post-injury interval, and therapeutic target [124,125]. This has direct translational relevance: preclinical dosing regimens optimized in male-only cohorts, which remain common in the

TBI-cannabinoid literature reviewed in Sections 2.3 and 2.4, may not generalize to females, and clinical eCB biomarker studies performed in mixed-sex cohorts without hormonal stratification risk obscuring clinically meaningful subgroups. Future studies should therefore move beyond treating sex as a covariate and examine how sex and hormonal status modify ECS signaling across the temporal course of TBI. Integrating molecular and lipidomic measures with inflammatory and functional outcomes will be essential to determine whether these differences influence therapeutic responsiveness and should inform the design of ECS-targeted interventions.

2.5.6. Peripheral and Systemic Endocannabinoid Responses to TBI

TBI is increasingly recognized as a systemic disorder rather than an isolated cerebral event [126]. The primary cerebral insult can trigger autonomic and neuroendocrine disturbances, release damage-associated signals, cause BBB dysfunction, and drive systemic inflammatory responses that extend to peripheral immune and vascular compartments and, in severe injury, may affect multiple organs [127–130]. The ECS is well positioned within this brain-periphery interface because CBRs, eCBs, and their metabolic enzymes are expressed not only in the CNS but also in circulating immune cells, vascular tissues, and peripheral organs. Nevertheless, the specific contribution of peripheral ECS signaling to TBI remains considerably less defined than its central actions, and evidence from general trauma populations should be distinguished from studies performed specifically in TBI.

Human studies demonstrate dynamic changes in circulating endocannabinoid signaling following traumatic injury, with peri-traumatic serum AEA and 2-AG concentrations showing distinct temporal patterns and associations with injury-related and long-term clinical outcomes [73,131]. In a prospective cohort of trauma survivors, Fitzgerald et al. measured serum AEA and 2-AG during the acute post-injury period and at approximately six months. Higher acute 2-AG concentrations predicted greater depressive symptom severity at follow-up, whereas acute AEA and later AEA/2-AG concentrations were not significant predictors. These findings were notable because they contradicted the expectation that greater circulating endocannabinoid signaling would necessarily be associated with improved stress adaptation, suggesting instead that elevated 2-AG after trauma may reflect injury-related ECS recruitment or dysregulation. However, these patients sustained heterogeneous traumatic injuries and should not be interpreted as a TBI-specific cohort [73].

Related prospective work further demonstrated that associations between peri-traumatic ECS signaling and subsequent clinical outcomes are heterogeneous. In a prospective cohort of 170 individuals hospitalized after traumatic injury, serum AEA concentrations measured during hospitalization were significantly higher in individuals who subsequently met diagnostic criteria for PTSD, whereas associations between 2-AG and later PTSD severity differed across population subgroups [72]. More recent work in an independent cohort of 100 trauma survivors found that higher peri-traumatic 2-AG was associated with greater PTSD symptom severity, pain severity, and poorer functional engagement 6–10 months later, although the association with PTSD did not survive correction for multiple comparisons and previously reported associations with depression were not replicated [132]. These observations indicate that elevated circulating eCB concentrations following trauma should not be interpreted as inherently protective; rather, their biological and prognostic significance appears to depend on the specific endocannabinoid, clinical outcome, and population characteristics studied.

Ahluwalia et al. reported preliminary evidence of altered endocannabinoid concentrations following human TBI. They compared CSF from eight patients with TBI with samples from six patients with normal pressure hydrocephalus, and plasma from seven patients with TBI with samples from nine healthy controls. Plasma AEA and 2-AG concentrations

were lower during TBI, whereas CSF showed lower 2-AG but higher AEA concentrations. Complementary experiments in a mouse controlled cortical impact model demonstrated increased FAAH, MAGL, and COX-2 expression in the choroid plexus and cerebral cortex. These observations suggest an association between altered endocannabinoid homeostasis and post-traumatic pathology, but do not establish that the lipid changes cause barrier dysfunction or neurological deficits. The small human cohorts and use of patients with normal pressure hydrocephalus as CSF controls also limit interpretation [77].

Recent lipidomic work further suggests that the peripheral response to mTBI extends beyond the canonical endocannabinoids AEA and 2-AG. Richter et al. profiled more than 80 plasma endolipids before and after single and repeated mTBI in male and female rats and identified marked sex- and injury-dependent changes in the circulating endolipidome. After the first head injury, 32% of measured plasma endolipids changed significantly in males compared with only 8% in females, whereas after a second injury the next day, 11% and 15% were altered in males and females, respectively. Notably, eicosapentaenoic acid and docosapentaenoic acid, fatty-acid precursors of pro-resolving mediators, increased in males following the first injury but not in females. In contrast, the canonical endocannabinoids AEA and 2-AG did not show significant acute pre- versus post-injury changes within either sex during the sampling intervals examined. These findings demonstrate that the circulating lipid response to mTBI is broader than changes in AEA and 2-AG alone and is influenced by sex, injury number, and sampling time. Because these measurements were obtained from plasma, however, they should not be interpreted as direct evidence of corresponding changes in the CNS ECS [122].

The distinction between central and peripheral endocannabinoid pools is particularly important when interpreting circulating biomarkers during TBI. In a mouse closed-head injury model, Panikashvili et al. demonstrated a rapid increase in 2-AG within the injured cerebral hemisphere, with concentrations significantly elevated by 1 h, reaching approximately tenfold above control levels at 4 h and remaining elevated at 24 h. Administration of exogenous 2-AG reduced brain edema, infarct volume and hippocampal neuronal loss and improved early neurological recovery [39]. In a subsequent study using the same experimental injury paradigm, 2-AG also reduced BBB permeability and suppressed the early expression of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6 [133]. These findings support local cerebral 2-AG mobilization as part of the endogenous response to experimental TBI. However, they do not establish that changes in circulating 2-AG originate from the brain or have equivalent biological significance. This distinction is particularly relevant given that higher circulating 2-AG after traumatic injury has been associated with adverse long-term outcomes in human trauma cohorts, emphasizing that central and peripheral eCB measurements should not be considered interchangeable.

Peripheral immune cells provide an important interface through which ECS signaling may influence secondary brain injury. During TBI, circulating leukocytes and monocyte-derived macrophages are recruited to injured brain tissue, where they contribute to the evolving neuroinflammatory response alongside resident microglia. In a mouse controlled cortical impact model, Braun et al. demonstrated increased CB_2R expression in infiltrating $CD11b^{+}CD45^{high}$ myeloid cells beginning approximately 72 h after injury. Pharmacological activation of CB_2R with the selective agonist GP1a reduced macrophage infiltration and was associated with decreased expression of pro-inflammatory macrophage markers and increased expression of markers associated with an alternatively activated phenotype. These changes were accompanied by reduced expression of inflammatory mediators, including TNF-α, IL-1β, IL-6, C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 10 (CXCL10), and inducible nitric oxide synthase (iNOS), as well as reduced cerebral edema, improved cerebral blood flow, and improved neurological outcomes. Together, these

findings identify infiltrating myeloid cells as an important CB_2R-responsive component of the post-traumatic inflammatory response and provide a mechanism through which ECS modulation may influence the interaction between peripheral immunity and secondary brain injury [134].

The interaction between ECS-dependent immune regulation and the cerebral vasculature is further supported by experimental manipulation of CB_2R during TBI. In a mouse controlled cortical impact model, Amenta et al. showed that pharmacological CB_2R stimulation with the selective agonists O-1966 or JWH-133 attenuated several components of the acute neurovascular inflammatory response, including TNF-α protein, intercellular adhesion molecule 1 (ICAM-1) and iNOS expression, and BBB permeability. Conversely, pharmacological CB_2R blockade increased TNF-α expression, while genetic deletion of CB_2R exacerbated TNF-α, ICAM-1, and iNOS expression and increased BBB permeability after injury. Because ICAM-1 contributes to leukocyte adhesion to the vascular endothelium and subsequent transendothelial migration, these findings support a role for CB_2R signaling at the immune–vascular interface during TBI. However, the cellular contribution cannot be attributed exclusively to peripheral immune cells, because CB_2R is also expressed by activated resident microglia and the study did not fully distinguish the relative contributions of peripheral and CNS-resident CB_2R-expressing populations [98].

Endocannabinoid metabolism provides an additional link between cannabinoid signaling and inflammatory lipid pathways. Hydrolysis of 2-AG by MAGL terminates 2-AG-mediated cannabinoid receptor signaling while generating AA, which can subsequently serve as a substrate for eicosanoid synthesis. Experimental disruption of MAGL has shown that this pathway is a major source of AA for prostaglandin production in the brain, positioning MAGL at a metabolic intersection between endocannabinoid and neuroinflammatory signaling [135]. Importantly, MAGL-dependent regulation of 2-AG and AA is not restricted to the CNS; pharmacological inhibition of MAGL alters these lipid pools in several peripheral tissues, including the spleen, lung, and liver [107]. Thus, systemic targeting of MAGL in TBI could potentially modify both central and peripheral lipid signaling, although the contribution of these peripheral metabolic effects to TBI outcomes has not been directly established. Other 2-AG-hydrolyzing enzymes may also influence secondary injury. In a mouse TBI model, treatment with the ABHD6 inhibitor WWL70 reduced BBB dysfunction, neurodegeneration, and inflammatory responses and improved functional recovery [136]. Together, these findings illustrate that ECS-metabolizing enzymes can influence inflammatory and neurovascular processes in addition to regulating cannabinoid receptor ligand availability.

Evidence from other disease models illustrates interactions between microbial metabolites and peripheral ECS regulation. In a study of Duchenne muscular dystrophy, sodium butyrate reduced skeletal muscle inflammation and improved autophagy-related abnormalities in mdx mice. In lipopolysaccharide-stimulated C2C12 myoblasts, it also prevented dysregulation of microRNAs targeting *Cnr1* through mechanisms involving GPR109A and PPARγ [137]. Whether comparable mechanisms contribute to systemic responses during TBI remains to be established. Taken together, current evidence supports a bidirectional model of ECS involvement during TBI. The injured brain generates local changes in endocannabinoid signaling while simultaneously triggering systemic immune, vascular, endocrine, and metabolic responses. Circulating AEA, 2-AG, and related endolipids may consequently reflect contributions from multiple tissues rather than serving as direct proxies for cerebral ECS activity. In parallel, peripheral CB_2R-expressing immune cells can enter injured brain tissue and influence inflammatory and vascular responses, while systemic modulation of endocannabinoid metabolism can affect interconnected cannabinoid and eicosanoid pathways. The peripheral ECS should therefore be considered part of a broader brain-body response to injury rather than an independent compartment.

Important gaps remain, particularly in humans. Most longitudinal studies of circulating eCBs have examined heterogeneous trauma populations rather than well-phenotyped TBI-only cohorts, whereas direct human comparisons of plasma and CSF endocannabinoid profiles remain small. The cellular and tissue sources of circulating eCBs during TBI are unresolved, and it remains unclear whether peripheral changes actively modify secondary injury, represent compensatory responses, or primarily serve as biomarkers of injury severity and systemic stress. Moreover, despite the established multi-organ consequences of TBI involving cardiovascular, pulmonary, gastrointestinal, hepatic, renal, endocrine, and immune systems, direct evidence demonstrating ECS-dependent regulation of these individual extracranial complications during TBI remains insufficient.

Future studies should therefore integrate serial plasma and, where clinically available, CSF endocannabinoid/endolipid profiling with peripheral immune phenotyping, BBB and endothelial biomarkers, inflammatory mediators, neuroimaging, injury characteristics, and longitudinal neurological outcomes. Parallel assessment of central and peripheral compartments will be particularly important for determining whether circulating ECS signatures provide information about cerebral pathology or instead capture distinct systemic responses to trauma. Resolving these relationships may establish whether peripheral ECS components can function as clinically accessible biomarkers, therapeutic targets, or modifiers of the systemic complications that contribute to TBI outcome.

3. Molecular Pathophysiology of TBI

The primary injury occurs at the point of impact and represents direct mechanical damage to neuronal, glial, and vascular elements [9]. This includes membrane disruptions, axonal shearing, and immediate disturbances in ionic balance [138]. Although the primary damage is mostly irreversible, it triggers a series of biochemical and molecular reactions that lead to secondary brain injury, which is the focus of acute clinical treatment [9].

Secondary injury evolves through a complex interplay of excitotoxic, ischemic, inflammatory, and cytotoxic processes that unfold over time and exacerbate the initial injury [139]. One of the earliest and most significant mechanisms is the excessive release of excitatory neurotransmitters, especially glutamate and aspartate, following the initiating trigger [140]. Cerebral microdialysis in patients with severe TBI has revealed elevated extracellular excitatory amino acid concentrations, particularly in association with secondary ischemia and focal contusions [141]. Excessive glutamate receptor activation can promote calcium-dependent neuronal injury, as demonstrated in cultured cortical neurons [142,143]. Experiments in cultured neurons further show that extrasynaptic NMDA receptor activation can engage cell-death pathways [144]. Concurrently, potassium efflux from damaged neurons and its uptake by astrocytes disrupt ionic equilibrium, leading to cellular swelling and further injury progression [145].

These excitotoxic processes are closely related to metabolic dysfunction and mitochondrial impairment, creating a self-reinforcing loop of neuronal stress [146]. Experimental TBI studies have documented mitochondrial dysfunction, disturbances in energy metabolism, and oxidative damage, supporting the role of mitochondrial impairment in secondary neuronal injury [147,148]. Importantly, these processes do not occur in isolation but constantly interact with inflammatory and vascular responses [149].

Neuroinflammation is a crucial aspect of this secondary injury cascade and arises quickly during TBI [150]. Activated microglia and astrocytes release numerous inflammatory mediators, including cytokines, chemokines, neurokinins, and growth factors, contributing to local and systemic reactions [151]. Among these mediators, interleukins have a particularly significant role. During TBI, increased levels of cytokines such as Interleukin-6 (IL-6) and Interleukin-10 (IL-10) have been associated with the degree of

perilesional edema and mortality [152]. Notably, these cytokines play multifaceted, context-dependent roles [151]. Inflammatory signaling can also support repair in specific contexts. In a mouse TBI model, experimentally induced microglial turnover generated repopulating microglia that supported brain repair and cognitive recovery through an IL-6-dependent mechanism [153]. These findings illustrate that inflammatory responses during TBI can have both damaging and reparative effects.

The inflammatory response extends beyond the central nervous system [139,151]. Systemic inflammation and multi-organ dysfunction are often observed during TBI, suggesting that brain injury triggers a broader physiological response, including peripheral immune activation [154,155]. This systemic aspect further intensifies the secondary injury cascade and complicates the overall understanding of TBI pathophysiology.

Cerebral ischemia is another significant factor contributing to secondary brain injury and is closely tied to both vascular disruption and metabolic failure [156]. The primary injury often causes immediate disturbances in cerebral circulation, reducing blood flow and causing tissue hypoxia [157]. Acute ischemic stroke can complicate moderate-to-severe TBI and is associated with poorer functional and cognitive outcomes [158]. This ischemic damage is made worse by conditions such as low blood pressure, hypoxia, increased intracranial pressure, cerebral edema, and microvascular injury [159].

In a study of patients with severe head injury, Martin et al. (1997) described three cerebral hemodynamic phases: hypoperfusion, hyperemia, and vasospasm [160]. An initial phase is marked by hypoperfusion and reduced cerebral blood flow immediately after the injury. This is followed by an intermediate phase, usually within the first few days, during which hyperemia and increased blood flow may be noted. In the later stages, a vasospastic phase can emerge, characterized by a significant drop in cerebral perfusion [160]. In summary, these observations emphasize that TBI pathophysiology is governed by an interconnected network of excitotoxic, metabolic, inflammatory, and vascular mechanisms. Rather than following a linear progression, these processes create a self-amplifying system where each element reinforces the others. Understanding this complex interplay is essential for developing effective therapeutic strategies to limit secondary injury and improve clinical outcomes.

3.1. Cell Death in the CNS

Neuronal loss during TBI begins almost immediately through necrotic cell death and persists for several months post-trauma via both necrotic and apoptotic pathways [161]. The primary injury creates a contused region, referred to as the primary lesion or infarct, which is encircled by the pericontusional penumbra, an area adjacent to the primary lesion that is susceptible to additional neurodegeneration. The development of the pericontusional penumbra is largely driven by secondary injury mechanisms, and it has long been considered a potential target for interventions to prevent or mitigate further damage [162]. Current research regarding cannabinoids in the context of traumatic CNS cell death has demonstrated efficacy in two primary areas: the reduction in neurodegeneration and the decrease in lesion volume [17].

Neurodegeneration has been notably reduced in murine models using CB_2R agonists and inhibitors of FAAH and MAGL [52,110,163]. Additionally, Tchantchou et al. (2014) showed that FAAH inhibition increased expression of the anti-apoptotic protein BCL-2 [52].

In mouse brain preparations, MAGL accounted for approximately 85% of measured 2-AG hydrolysis, while ABHD6 and α/β-hydrolase domain-containing protein 12 (ABHD12) accounted for most of the remaining activity [104]. Tchantchou and Zhang (2013) reported that treatment with the ABHD6 inhibitor WWL70 reduced lesion volume and neurodegeneration in a CCI mouse model [136]. Notably, a CB_1R antagonist negated the

protective effects on lesion volume, while antagonism of both CB_1R and CB_2R blocked the neuroprotective effects [136]. ABHD12 has additional lipid-metabolic functions that may influence inflammatory responses. In mice, loss of ABHD12 caused accumulation of brain lysophosphatidylserines, followed by age-dependent microglial activation and neurological abnormalities [164]. Subsequent work linked ABHD16A-ABHD12-dependent lysophosphatidylserine metabolism to macrophage inflammatory responses [165]. These findings were obtained outside TBI models and do not establish a therapeutic benefit of ABHD12 inhibition during TBI.

In summary, this body of evidence suggests that inhibitors of eCB hydrolysis confer protection against TBI-induced cell death, implicating both CB_1R and CB_2R; however, distinctions among eCBs remain to be elucidated. Few studies have investigated the interactions between AEA and 2-AG in laboratory models of TBI. One investigation using a model of focal cerebral ischemia showed that concurrent administration of AEA and 2-AG reduced infarct size in rats, but without additional benefit beyond each substance alone [166]. Given recent advances in dual FAAH/MAGL inhibitors, combined inhibition of these enzymes during TBI may yield further insights into the interplay between AEA and 2-AG in TBI-induced cell death [167,168].

3.2. Excitotoxicity and Its Implications in TBI

Excitotoxicity, a pathological process resulting from excessive activation of glutamate receptors, poses significant challenges following brain injuries [169]. Past therapeutic efforts aimed at limiting excitotoxicity during TBI have included pharmacological antagonism of NMDA receptors, based on the rationale that excessive NMDA receptor activation contributes to excitotoxic neuronal injury [170]. Among the compounds investigated in TBI, dexanabinol (HU-211) progressed from experimental studies to clinical evaluation. Dexanabinol, a non-competitive NMDA receptor antagonist, showed beneficial effects on motor and memory outcomes in an experimental model of closed-head injury [171]. In a subsequent Phase II randomized, placebo-controlled clinical trial in patients with severe TBI, dexanabinol was associated with acute physiological effects, including improved control of intracranial pressure and cerebral perfusion pressure [172]. However, these findings did not translate into sustained clinical efficacy, as a larger Phase III randomized, placebo-controlled trial did not demonstrate improvement in long-term neurological outcomes [28].

Recent research has therefore increasingly examined how modulation of the ECS may influence glutamatergic signaling and excitotoxic mechanisms during TBI [17]. Among the eCBs, 2-AG has emerged as a focal point because of its complex role in maintaining glutamate receptor integrity [173].

Experimental studies have examined how cannabinoid-related interventions affect glutamate receptor expression in animal models of TBI [27,110,174]. At 8 days after the first injury, JZL184 counteracted reductions in hippocampal GluA1, GluN2A, and GluN2B expression, without significantly affecting GluA2 or GluN1 expression. At 30 days, treatment also counteracted the reduction in GluA2, but did not suppress elevated GluN1 expression [110]. The CB1R antagonist rimonabant did not reverse the injury-related decrease in mGluR1 expression but reversed the decrease in mGluR5 expression [174]. These studies indicate that alterations in glutamatergic signaling can persist beyond the acute post-injury period [110,174]. These studies examined different aspects of glutamatergic signaling. In mice subjected to repetitive mild closed-head injury, Zhang et al. reported reduced hippocampal GluA1 protein expression, which JZL184 treatment attenuated [110]. In rats subjected to lateral fluid percussion injury, Mayeux et al. found an increased ratio of GluA1 phosphorylated at Ser845 to total GluA1 in the cortex at 10 days post-injury;

JZL184 attenuated this increase [27]. Changes in receptor abundance and phosphorylation represent distinct endpoints and should not be interpreted as directly conflicting findings.

eCBs are well-documented for their capacity to inhibit glutamate release from presynaptic terminals, particularly 2-AG, which has garnered attention for its modulatory role in electrochemical neurotransmission [175,176]. The inhibition of MAGL has been shown to provide a protective effect against injury-induced increases in both the frequency and amplitude of excitatory postsynaptic currents (EPSCs) within pyramidal neurons located at the site of injury [27]. This observation may suggest potential alterations in presynaptic neurotransmitter release mechanisms or modifications in postsynaptic responsiveness [177]. Furthermore, MAGL inhibition has conferred protection against deficits in long-term potentiation (LTP) at hippocampal CA3-CA1 synapses [110], indicating that restoring glutamate receptor function may play a crucial role in mitigating memory impairments associated with TBI. Ultimately, TBI-induced excitotoxicity triggers a complex cascade that culminates in the release of harmful ROS. Antioxidants are known to thwart oxidative damage caused by sudden spikes in ROS levels. Notably, eCBs have been linked to the neuroprotective promotion of antioxidant production; for instance, administering exogenous 2-AG following injury has been shown to elevate antioxidant levels [133].

In conclusion, the evidence points to MAGL as a promising target for counteracting the adverse effects of excitotoxicity following brain injury through multiple complementary molecular pathways. This highlights the potential of therapeutic strategies that harness the eCB system's protective properties to mitigate the consequences of excitotoxic brain damage.

3.3. Neuroinflammation and Its Implications in TBI

Hydrolysis of AEA and 2-AG releases arachidonic acid (AA), a substrate for eicosanoid biosynthesis [178]. Through a distinct oxidative pathway, COX-2 and downstream synthases can convert AEA and 2-AG into prostaglandin ethanolamides and glycerol esters, respectively [179]. These metabolic routes link endocannabinoid turnover to the production of additional lipid mediators. Pharmacological modulation of the ECS has reduced inflammatory pain in rodents [180] and attenuated inflammatory responses in a mouse model of multiple sclerosis [181]. In experimental TBI, FAAH inhibition attenuated inflammatory microglial/macrophage responses [52], while exogenous 2-AG reduced pro-inflammatory cytokine mRNA expression [133].

Activated microglia have been implicated in the neuroinflammatory response during TBI [182]. Microglial activation during TBI has traditionally been characterized using an M1/M2 framework, in which M1-like states are associated predominantly with pro-inflammatory responses, whereas M2-like states are associated with anti-inflammatory and reparative functions. Experimental studies, however, show that these responses are dynamic and not mutually exclusive, with microglia/macrophages exhibiting temporally changing M1- and M2-associated markers, as well as mixed phenotypes, during TBI [182,183]. Thus, modulating inflammatory microglial responses during TBI is a potential therapeutic strategy. Inhibition of MAGL has been shown to attenuate TBI-induced microglial activation [110,184], whereas treatment with the ABHD6 inhibitor WWL70 was associated with a shift toward anti-inflammatory and reparative microglial/macrophage phenotypes in experimental TBI, as characterized using the original study's M1/M2 framework [136]. However, a subsequent study in activated microglia showed that WWL70 reduced prostaglandin E_2 production through an ABHD6-independent mechanism, indicating that its anti-inflammatory effects cannot be attributed exclusively to ABHD6 inhibition [185]. A straightforward interpretation is that inhibiting 2-AG breakdown reduces AA levels, thereby mitigating pro-inflammatory mediator production [186]. Adverse effects of cannabinoid signaling have also been reported in experimental models of nephropathy [187] and

cardiomyopathy [188]. These adverse effects are model- and receptor-dependent. For example, AEA induced oxidative stress and cell death through CB_1R-associated mechanisms in cultured human cardiomyocytes [188]. Nonetheless, inhibition of FAAH has similarly shown protective effects against TBI-induced microglial activation [186], as has activation of CB_2R [163]. Therefore, it is critical to distinguish 2-AG's potential contributions to pro-inflammatory processes from its role as a precursor to AA production and its anti-inflammatory effects mediated through cannabinoid receptors in the context of TBI.

Inhibition of the enzymes responsible for the degradation of eCBs has also resulted in decreased levels of pro-inflammatory mediators induced by TBI [27,136]. Reduced expression of inflammatory enzymes, including cyclooxygenase-2 (COX-2), which participates in prostanoid synthesis, and inducible nitric oxide synthase (iNOS), which produces nitric oxide, has been reported following treatment with WWL70 [136] and FAAH inhibition [52] in experimental TBI. Additionally, decreases in messenger RNA levels of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) have been documented after treatment with exogenous 2-AG [133]. These findings appear paradoxical, given 2-AG's potential for rapid oxidation and its subsequent role in eicosanoid production. However, exogenous 2-AG has been shown to reduce TBI-induced activation of nuclear factor kappa B (NF-κB) (associated with cytokine production) in wild-type mice but not in *Cnr1*-knockout mice, indicating that the protective effects of exogenous 2-AG are mediated through CB_1Rs [189]. Table 2 outlines the mechanisms by which cannabinoids influence the neuronal, inflammatory, and vascular components of TBI. Importantly, cannabinoid-mediated effects are not pathway-specific but rather span multiple interconnected domains, supporting a systems-level mechanism of action.

Table 2. Cannabinoid-mediated modulation of TBI pathophysiological pathways (preclinical evidence). 2-AG, 2-arachidonoylglycerol; BBB, blood–brain barrier; CB_1R/CB_2R, cannabinoid receptor type 1/type 2; COX-2, cyclooxygenase-2; eCB, endocannabinoid; EPSCs, excitatory postsynaptic currents; FAAH, fatty acid amide hydrolase; HSP70, heat shock protein 70; iNOS, inducible nitric oxide synthase; IL-1β/IL-6, interleukin-1β/interleukin-6; LTP, long-term potentiation; MAGL, monoacylglycerol lipase; NF-κB, nuclear factor κB; ROS, reactive oxygen species; TBI, traumatic brain injury; TNF-α, tumor necrosis factor α; GluA1, AMPA receptor subunit 1; BCL-2, B-cell lymphoma 2 protein. The downward arrow (↓) indicates a decrease, and the upward arrow (↑) indicates an increase, relative to the corre-sponding control group in the cited study.

Pathophysiological Domain	Intervention Strategy	Mechanistic Target(s)	Key Observed Effects	Proposed Functional Outcome	Refs.
Cell death	MAGL inhibition (JZL184), FAAH inhibition (PF3845), CB_2R agonists (O-1966)	eCB accumulation, CB_2R signaling	↓ lesion volume, ↓ neurodegeneration, ↑ BCL-2, HSP70	Enhanced neuronal survival	[52,110,163]
Excitotoxicity/ synaptic dysfunction	2-AG administration, CB_1R modulation, enzyme inhibition	Presynaptic CB_1R signaling, glutamate receptor regulation	Restoration of glutamate receptor function, protection of LTP and EPSC	Stabilization of synaptic transmission	[18,27,57]
Oxidative stress	eCB elevation (2-AG), indirect antioxidant effects	ROS modulation, lipid signaling	↑ antioxidant response, ↓ oxidative damage	Protection against mitochondrial dysfunction	[52,133]
Neuroinflammation	CB_2R agonists, FAAH/MAGL inhibition, 2-AG elevation	Microglial CB_2R activation, NF-κB signaling	↓ TNF-α, IL-1β, IL-6; ↓ COX-2 and iNOS; ↓ microglial activation	Attenuation of inflammatory response	[163,184,189]
BBB integrity	2-AG signaling, cannabinoid modulation	Endothelial signaling, inflammatory regulation	↓ BBB permeability, improved vascular integrity	Reduced edema and secondary injury	[136,189]

Table 2. *Cont.*

Pathophysiological Domain	Intervention Strategy	Mechanistic Target(s)	Key Observed Effects	Proposed Functional Outcome	Refs.
Synaptic plasticity and recovery	CB_1R-dependent modulation, enzyme inhibition	Retrograde signaling pathways	Preservation of LTP, GluA1 expression, EPSC stabilization	Improved cognitive recovery	[27,110]
Neurovascular response	CB_2R agonism with GP1a	CB_2R signaling and modulation of macrophage inflammatory phenotypes	Improved cerebral blood flow; reduced edema	Improved neurobehavioral recovery	[134]

4. Clinical Evidence and Translational Status of ECS-Targeted Approaches in TBI

Clinical evaluation of cannabinoid-related interventions in TBI has remained limited, with controlled human studies principally involving dexanabinol (HU-211) and the dual CB_1/CB_2 receptor agonist KN38-7271. Dexanabinol is the non-psychotropic synthetic enantiomer of the potent cannabinoid agonist HU-210; however, unlike HU-210, it does not exert its effects through conventional cannabinoid receptor activation and has instead been characterized primarily by non-competitive NMDA receptor antagonism together with anti-inflammatory and antioxidant properties. Following encouraging findings in an early Phase II study, dexanabinol was evaluated in a multicenter Phase III randomized, placebo-controlled trial involving 861 patients with severe TBI who received a single 150-mg intravenous dose or placebo within 6 h of injury. Although dexanabinol was generally well tolerated, it did not improve six-month neurological outcome assessed using the extended Glasgow Outcome Scale, nor did it significantly improve intracranial pressure control or quality of life [28]. A more direct pharmacological test of cannabinoid receptor activation came from KN38-7271, a dual CB_1/CB_2 receptor agonist evaluated in a randomized, double-blind, placebo-controlled Phase IIa trial involving 97 patients with severe TBI. Administration within 4.5 h of injury was associated with improved early survival and fewer extreme disturbances in intracranial and cerebral perfusion pressures; however, the survival difference was no longer evident at six months, and the study was not followed by confirmatory late-phase evidence establishing clinical efficacy [29]. Collectively, these trials demonstrate that cannabinoid-related compounds have reached controlled clinical testing in acute TBI, but neither approach has established sustained therapeutic efficacy. They also highlight an important mechanistic distinction: the negative Phase III dexanabinol trial should not be interpreted as a direct clinical test of CB_1R or CB_2R activation, whereas KN38-7271 more directly evaluated cannabinoid receptor agonism.

More recent human evidence has emerged from observational studies examining cannabis exposure at the time of TBI, although these data should be distinguished from controlled therapeutic intervention. In a large retrospective cohort of patients presenting with acute TBI, recreational cannabis exposure, identified by a positive urine drug screen, was not associated with a significant difference in mortality but was associated with a higher likelihood of discharge home, lower modified Rankin Scale scores at discharge, and shorter hospital stays; several associations remained significant after multivariable adjustment [190]. In contrast, analysis of severely injured patients with TBI using the American College of Surgeons Trauma Quality Improvement Program found no significant differences between THC-positive and THC-negative patients in mortality, length of stay, cardiac arrest, pulmonary embolism, deep-vein thrombosis, or acute respiratory distress syndrome, although hemorrhagic stroke occurred less frequently in the THC-positive group [191]. Recent findings also suggest that associations may differ by the clinical outcome examined. In a retrospective analysis of 72,901 adults with blunt TBI from the 2020 American College

of Surgeons Trauma Quality Improvement Program, an isolated positive cannabinoid screen was independently associated with increased odds of delirium during hospitalization after multivariable adjustment (aOR 1.326, $p \leq 0.001$) [192]. These findings should be interpreted cautiously, as retrospective toxicology-based studies cannot establish a causal neuroprotective effect of cannabinoids. A positive THC screen does not define the dose, timing, frequency, cannabinoid composition, or route of cannabis exposure, and residual differences between exposed and unexposed populations may remain despite statistical adjustment. Moreover, findings from broader trauma populations are not necessarily specific to TBI; for example, a large propensity-matched analysis of 28,028 cannabis-positive and 28,028 cannabis-negative trauma patients found no significant difference in in-hospital mortality or most complications [193]. Collectively, these findings expand the human evidence base but do not establish a neuroprotective or detrimental effect of cannabis exposure during TBI. Their interpretation is constrained by the observational nature of the studies and by reliance on toxicological evidence of exposure, which does not establish cannabinoid dose, timing relative to injury, frequency of use, route of administration, or THC/CBD composition. Residual differences in demographic characteristics, injury patterns, comorbidities, and concomitant substance exposure may also contribute to the reported associations. Accordingly, these studies should be distinguished from controlled pharmacological manipulation of the ECS and cannot establish whether the observed outcomes are mediated directly through CB_1R, CB_2R, or other cannabinoid-sensitive pathways.

5. Discussion

The ECS, including endogenous ligands and potential entourage effects from other lipid mediators, can be further modulated through strategies such as antagonism and allosteric regulation, which may influence functional selectivity and, consequently, TBI outcomes. Targeting this system with endogenous, plant-derived, or synthetic cannabinoids presents a promising avenue for developing therapeutic strategies for TBI. A critical step in understanding the ECS's role in TBI involves an in-depth analysis of ligands that target cannabinoid receptors and of the enzymes that regulate eCB levels. CBD-containing interventions have shown beneficial effects in experimental TBI models [59–61]. Across preclinical studies, modulation of the ECS has been associated with attenuation of several components of secondary injury, including excitotoxicity, neuroinflammation, oxidative stress, and BBB dysfunction [17]. However, these findings should not be interpreted as evidence that ECS activation is uniformly neuroprotective. Rather, the consequences of ECS modulation appear to depend on the ligand and molecular target involved, cellular context, injury phase, treatment timing and dose, and biological factors such as sex and genetic background. These effects are observed across multiple intervention strategies, including eCB supplementation, enzyme inhibition, and receptor-specific modulation, resulting in improved histological and functional outcomes. Additionally, research must focus on how TBI affects cannabinoid receptors, eCB levels, and the enzymes that regulate eCB metabolism [39–41].

Another important area for future therapeutic exploration is non-CB_1R/CB_2R targets, such as TRPV1 receptors, and bridging preclinical efficacy and clinical outcomes. Moreover, investigating alternative approaches to modulate CB_1R and CB_2R signaling may further refine therapeutic outcomes. In this context, plant-derived compounds remain an underexplored yet potentially valuable source of multi-target therapeutic agents. However, the involvement of cannabinoid and non-cannabinoid targets also emphasizes the need to distinguish broad cannabinoid pharmacology from selective modulation of defined ECS pathways when interpreting therapeutic effects.

Despite substantial preclinical evidence, translation of ECS-targeted approaches to human TBI remains limited. As summarized in Section 4 and Table 3, controlled clinical studies have not established sustained therapeutic efficacy, while recent observational studies of cannabis or cannabinoid exposure have reported heterogeneous associations across mortality, functional outcomes, vascular complications, and delirium. These findings reinforce an important distinction between controlled pharmacological modulation of defined ECS targets and uncontrolled cannabinoid exposure in clinical populations. Consequently, associations between pre-injury cannabinoid exposure and clinical outcomes cannot be interpreted as evidence that cannabinoid administration is therapeutically effective or that the observed effects are mediated specifically through CB_1R or CB_2R. Future studies integrating patient stratification, biomarker-guided interventions, and mechanism-informed pharmacological approaches may improve clinical translation.

Several factors may contribute to the gap between preclinical findings and clinical outcomes, including injury heterogeneity, treatment timing, dosing, CNS exposure, and pharmacological selectivity. However, the contribution of each factor to the outcomes of individual cannabinoid trials in TBI remains uncertain. Preclinical models typically involve controlled injury scenarios, consistent treatment timing, and uniform populations, which enable detailed mechanistic exploration. In contrast, clinical TBI encompasses substantial heterogeneity in injury mechanism, severity, anatomical distribution, age, sex, comorbidities, concomitant medications, and systemic complications, all of which may influence treatment response. Additionally, experimental interventions may influence multiple pathological processes in parallel, whereas clinical evaluation requires consideration of pharmacological selectivity, therapeutic exposure, and the appropriate treatment window. The timing dynamics of TBI make this translation even more challenging, as the relative impacts of excitotoxicity, inflammation, and metabolic processes change over time, such that the consequences of targeting a particular ECS component may differ across the acute, subacute, and chronic phases of injury. Therapeutic efficacy may therefore depend not only on the molecular target itself, but also on treatment timing, dose, duration of exposure, and the patient's biological characteristics.

Table 3. Human clinical and observational evidence for cannabinoid-related interventions and exposures in TBI. Abbreviations: ARDS, acute respiratory distress syndrome; CB_1R, cannabinoid receptor type 1; CB_2R, cannabinoid receptor type 2; CPP, cerebral perfusion pressure; DVT, deep-vein thrombosis; ICP, intracranial pressure; ISS, Injury Severity Score; LOS, length of stay; mRS, modified Rankin Scale; PE, pulmonary embolism; THC, Δ^9-tetrahydrocannabinol; TQIP, Trauma Quality Improvement Program; TBI, traumatic brain injury; ACS-TQIP, American College of Surgeons Trauma Quality Improvement Program; aOR, adjusted odds ratio; i.v., intravenous.

Ref.	Population	Intervention/ Exposure	Study Design	Main Findings	Key Limitations/ Interpretation
[28]	861 patients with severe TBI; 86 centers in 15 countries	Dexanabinol (HU-211), single 150-mg i.v. dose within 6 h of injury	Multicenter randomized, placebo-controlled Phase III trial	Dexanabinol was well tolerated but did not improve 6-month extended Glasgow Outcome Scale, ICP control, or quality of life.	Dexanabinol does not conventionally activate CB_1R/CB_2R; the negative trial therefore does not constitute a direct clinical test of cannabinoid-receptor agonism.
[29]	97 comatose patients with severe TBI at 14 European centers	KN38-7271, dual CB_1/CB_2 receptor agonist; 500 or 1000 µg within 4.5 h	Randomized, double-blind, placebo-controlled Phase IIa trial	Early survival was higher in the treatment groups, and critical ICP/CPP disturbances were less extreme/frequent; the survival difference was no longer evident at 6 months.	Small proof-of-concept trial; early signals were not sustained at 6 months and require confirmation in adequately powered trials.

Table 3. *Cont.*

Ref.	Population	Intervention/ Exposure	Study Design	Main Findings	Key Limitations/ Interpretation
[191]	13,266 adults with TBI and severe injury (ISS ≥ 16); 1377 THC+ patients propensity-matched to 1377 THC− patients	Pre-injury THC exposure identified by toxicology	Retrospective ACS-TQIP analysis with propensity-score matching	No significant differences in mortality, LOS, cardiac arrest, PE, DVT, or ARDS. Hemorrhagic stroke was less frequent in THC+ patients (0.5% vs. 1.5%; $p = 0.02$).	Observational exposure rather than therapeutic administration; toxicology does not establish dose, timing, frequency, or cannabis composition.
[193]	National trauma cohort; 28,028 cannabis-positive patients propensity-matched to 28,028 cannabis-negative patients	Cannabis positivity at initial trauma evaluation	Retrospective TQIP propensity-matched analysis	No difference in in-hospital mortality (3.2% vs. 3.2%) or hospital LOS; PE was slightly less frequent in cannabis-positive patients (0.4% vs. 0.5%).	General trauma population rather than a TBI-specific cohort; findings cannot be interpreted as evidence of therapeutic efficacy in TBI.
[190]	3729 acute TBI patients undergoing urine drug screening; 22.2% cannabis-positive	Pre-TBI recreational cannabis exposure identified by urine drug screen	Retrospective cohort study	Mortality did not differ significantly (3.9% vs. 4.8%); cannabis positivity was associated with higher discharge-home rates, lower discharge mRS scores, and shorter hospitalization, with several associations persisting after multivariable adjustment.	Observational study with substantial baseline differences between exposure groups; dose, timing, frequency, and composition of cannabis exposure were not standardized, precluding causal inference.
[192]	72,901 adults with blunt TBI in the 2020 ACS-TQIP database; 13.4% cannabinoid-positive	Cannabinoid-positive substance screen	Retrospective national database analysis	An isolated positive cannabinoid screen was independently associated with higher odds of in-hospital delirium (aOR 1.326; $p \leq 0.001$).	Observational association; cannabinoid type, dose, timing, frequency, and chronicity were not established, and residual confounding cannot be excluded.

A frequently overlooked aspect of TBI research is whether systemically administered drugs can penetrate the CNS effectively. Therapeutic interventions should therefore be evaluated not only by the administered dose but also by their ability to cross the BBB, achieve sufficient CNS exposure, and engage the intended molecular target. Additionally, TBI can disrupt the BBB, and human post-mortem evidence indicates that this disruption may persist beyond the acute injury phase [194]. Pharmacological selectivity is another challenge, as compounds targeting CB_1R, CB_2R, FAAH, MAGL, ABHD6, or related pathways may differ substantially in CNS penetration, duration of action, off-target activity, and peripheral effects. Moreover, modulation of eCB-metabolizing enzymes can alter interconnected lipid pathways rather than exclusively modifying cannabinoid receptor signaling. For example, hydrolysis of 2-AG by MAGL generates arachidonic acid, thereby linking endocannabinoid metabolism to downstream eicosanoid biosynthesis. Given the dose-dependent and frequently biphasic effects of cannabinoid-related compounds, it is essential to move beyond single-dose studies toward systematic evaluation of dose–response relationships, pharmacokinetics, CNS exposure, and target engagement.

6. Conclusions

TBI is a complex condition to manage due to its biological intricacies and patient variability. Although extensive preclinical evidence supports the therapeutic potential of targeting the ECS, translation into clinical settings has remained limited, emphasizing that ECS signaling should be considered context-dependent rather than uniformly neuroprotective. Future advances will require integration of mechanistic understanding with clinically applicable strategies that account for treatment timing and dosing, CNS target engagement, injury heterogeneity, sex, genetic variability, and central and peripheral ECS responses.

Defining which ECS components to target, in which biological context, and during which injury phase will therefore be critical to determining whether the therapeutic potential observed experimentally can translate into meaningful clinical benefit during TBI.

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Abbreviations

The following abbreviations are used in this manuscript:

TBI	Traumatic brain injury
ECS	Endocannabinoid system
eCBs	Endocannabinoids
AEA	Anandamide (*N*-arachidonoylethanolamine)
2-AG	2-Arachidonoylglycerol
CB_1R	Cannabinoid receptor 1
CB_2R	Cannabinoid receptor 2
CBD	Cannabidiol
MAGL	Monoacylglycerol lipase
FAAH	Fatty acid amide hydrolase
ABHD6	Alpha/beta-hydrolase domain-containing 6
ABHD12	α/β-hydrolase domain-containing protein 12
GPR	G-protein-coupled receptors
BBB	Blood–brain barrier
CNS	Central nervous system
mTBI	mild TBI
CCI	Controlled Cortical Impact
HU-211	Dexanabinol
NMDA	N-methyl-D-aspartate
TNF-α	Tumor necrosis factor alpha
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
PPARγ	Peroxisome proliferator-activated receptor γ
ROS	Reactive oxygen species
THC	Δ^9-Tetrahydrocannabinol
TRPV1	Transient receptor potential vanilloid 1

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