The CB2 Receptor as a Novel Therapeutic Target for Epilepsy Treatment

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Abstract: Epilepsy is characterized by repeated spontaneous bursts of neuronal hyperactivity and high synchronization in the central nervous system. It seriously affects the quality of life of epileptic patients, and nearly 30% of individuals are refractory to treatment of antiseizure drugs. Therefore, there is an urgent need to develop new drugs to manage and control refractory epilepsy. Cannabinoid ligands, including selective cannabinoid receptor subtype (CB1 or CB2 receptor) ligands and non-selective cannabinoid (synthetic and endogenous) ligands, may serve as novel candidates for this need. Cannabinoid appears to regulate seizure activity in the brain through the activation of CB1 and CB2 cannabinoid receptors (CB1R and CB2R). An abundant series of cannabinoid analogues have been tested in various animal models, including the rat pilocarpine model of acquired epilepsy, a pentylenetetrazol model of myoclonic seizures in mice, and a penicillin-induced model of epileptiform activity in the rats. The accumulating lines of evidence show that cannabinoid ligands exhibit significant benefits to control seizure activity in different epileptic models. In this review, we summarize the relationship between brain CB2 receptors and seizures and emphasize the potential mechanisms of their therapeutic effects involving the influences of neurons, astrocytes, and microglia cells. The unique features of CB2Rs, such as lower expression levels under physiological conditions and high inducibility under epileptic conditions, make it an important target for future research on drug-resistant epilepsy.

Keywords: cannabinoid receptor 2; epilepsy; cAMP; M-current; anti-inflammatory

1. Introduction

Epilepsy is the third most common chronic neurological disorder that affects over 70 million people worldwide [1]. Occurrence of epileptic seizure in different brain areas may lead to loss of consciousness, motor or sensory disorders, and emotional or cognitive dysfunction [2]. Despite much progress in medical treatment using antiseizure drugs to control epileptic seizures, it still remains at 30% of patients that fail to be controlled by or respond to antiseizure drugs [3]. Thus, there is an urgent need to develop new medicines to control refractory epilepsy.

More understanding of underlying mechanisms in epileptogenesis has identified cellular and molecular targets for new therapies, for example, anti-inflammatory drugs that can overcome the limitations of current drugs and provide symptomatic control of epileptic seizures [4]. Accumulating data have demonstrated that cannabinoid systems, including endocannabinoids, anandamide, and 2-arachidonoyl glycerol, and their targets, the cannabinoid receptor subtype 1 (CB1R) and subtype 2 (CB2R), appear to regulate seizure activity [5–13]. The rationale for the antiseizure effects of the cannabinoid system is that the CB2Rs (possibly also CB2Rs) are linked to an inhibitory G protein (Gi/o) signaling, which reduces neuronal excitability and/or neural synchronization. For example, the
activation of brain CB$_1$R modulates A-type K$^+$ channels and N- and P/Q-type voltage-gated Ca$^{2+}$ currents and stabilizes the membrane potentials [14,15], and it modulates presynaptic neurotransmitter release [16–18]. Furthermore, cannabidiol has been shown to not only reduce the frequency of seizures in animal models of epilepsy but also greatly decrease the frequency of drop seizures among children and adults with Lennox–Gastaut syndrome [19]. Based on these concepts, numerous cannabinoid analogues have been examined in a variety of animal models [5,8,11,20–23]. However, although cannabinoid ligands and CB$_1$R agonists possess some antiseizure effects, non-specific modulations of cannabinoid systems will limit their therapeutic use for treatment of human epilepsy because of their severe adverse effects, for example, THC (50 mg or more) has been shown to lead to anxiety, psychosis, heart attack, and irregular heart rhythm. Regularly taking large amounts of cannabis over a long period of time might cause a cannabinoid hyperemesis syndrome. Therefore, significant attention is currently being directed toward the possibility of developing medicines from compounds that can selectively activate CB$_2$Rs and have important potential therapeutic applications at doses that induce little or no CB$_1$R-mediated effects.

In this review, we summarize the current state of knowledge on CB$_2$R expression and function, which could serve as an important tool for intervention and control of seizure activity by modulating neuronal excitability and neuroinflammation.

2. CB$_2$R Expression and Inducible Feature

Cannabinoid receptor type 2 (CB$_2$R) is a plasma membrane G protein-coupled receptor that was characterized from spleen by Munro [24]. The expression and function of CB$_2$ in the brain have been debated due to early studies implying that CB$_2$Rs were missing in the central nervous system (CNS), since CB$_2$-R mRNA expression was not measured in rat brains by using in situ hybridization [24]. In accordance with this result, Northern blot analysis also failed to detect CB$_2$R mRNA in rat, mouse, and human brains [25–27]. RT-PCR experiments demonstrated abundant CB$_2$R expression among peripheral immune tissues, such as on spleen T cells and on macrophages, but barely measurable levels in rodent brains [25,26,28,29]. Little is revealed about CB$_2$ Rs receptor expression in microglia, astrocytes, and astrocytoma, and the activation of these receptors affecting cellular function and activity [28]. Based on the above research, CB$_2$Rs have been classically considered as peripheral cannabinoid receptors [24,30,31]. Recently, this concept of CB$_2$ deficiency within the brain has been challenged along with the identification of CB$_2$Rs widespread in the CNS, though they are expressed at lower densities than CB$_1$. Emerging evidence shows that significant CB$_2$R mRNA can be detected by ISH in cultured granule cells among the granule layer and Purkinje cell layer of the mouse cerebellum [29], in the mouse retina [32], and in the globus pallidus of non-human primates [30]. RT-PCR analysis has also been applied to distinguish CB$_2$ mRNA expression in multiple brain regions, including the retina [32], cortex [30,31,33,34], striatum [26,34], hippocampus [30], amygdala [33,34], brainstem [35], and cerebellum [36]. Furthermore, two CB$_2$ isoforms, CB$_{2A}$ and CB$_{2B}$, have been characterized in the rodent and human brain [31] along with a new CB$_2$ transcript that has been found in mouse and monkey B lymphocytes [37]. This suggests the possibility that CB$_2$R expression not only exists in peripheral tissues, but also in the brain. It has been reported that CB$_2$Rs modulate a variety of important processes in dopamine (DA)-related behaviors [38], including food intake [39–42], anxiety [33,43], depression [44], and schizophrenia-like behavior [34,45]. Recent evidences emerging from several laboratories, including ours, have indicated that brain CB$_2$Rs play a pivotal role in the reduction of cocaine, alcohol, and nicotine addiction [46–48]. Collectively, these lines of evidence strongly suggest an important role of CB$_2$R in the mesocorticolimbic system, as well as in various brain functions involving psychiatric, cognitive, and neurobiological activity. Compared to CB$_1$Rs, central CB$_2$Rs display the following unique features: (1) low expression grades, suggesting that they may not modulate neural functions under physiological conditions, (2) high pathological expression, meaning that under some pathological conditions (for example, addiction, stroke, stress, schizophrenia, inflammation, anxiety), CB$_2$R expression
increased in the brain [49], suggesting that the change of CB$_2$R expression/function is closely related to various mental and neurological diseases, and (3) post-synaptic localization, where CB$_2$Rs are chiefly expressed on neuronal terminals, especially on GABAergic terminals (presynaptic), which leads to some opposing effects after activation by these two receptor subtypes [51]. In consideration of these features, CB$_2$R is likely an important target for neuroprotection [52], and targeting CB$_2$Rs likely provide a novel therapeutic strategy for treating neuropsychiatric and neurological diseases without typical CB$_1$-mediated side-effects. However, to fulfill this possibility, an understanding of the functional effects of CB$_2$Rs in the brain is required. Unfortunately, the function of CB$_2$Rs in the CNS has not been well-established, and studies of the functional effects of CB$_2$Rs in neurons have ignited debate and controversy. A consensus has yet to emerge regarding the expression and function of CB$_2$Rs in midbrain ventral tegmental area (VTA) neurons, which are the source of mesocorticolimbic dopamine (DA) signaling. In our recent study, we found that functional CB$_2$Rs are expressed in VTA DA neurons, and the activation of these CB$_2$Rs reduced the excitability of DA neurons through both intrinsic and synaptic mechanisms [53].

3. Drug Resistance in Epilepsy

The occurrence of epilepsy is usually related to a disorder of excitatory and/or inhibitory neurotransmitters, such as upregulation of glutamate and acetylcholine, and downregulation of GABA and serotonin. According to this concept, about 40 anti-seizure drugs are used for symptomatic treatment of epilepsy [54]. However, over one third of epileptic patients are resistant to multiple antiseizure drug therapies. Drug-resistant epilepsy can be defined as a failure of multiple efficient treatments of tolerated, chosen, and appropriately used anti-epileptic drug guidelines [55]. Based on the inducement and hypothetical mechanisms of drug-resistant epilepsy, recent speculations of mechanisms of drug resistance include: (1) Drug target variation: drug targets evoke the alteration of neurotransmitter receptors, voltage-dependent ion channels, and transporters participating in the metabolic pathway involved in the metabolism of neurotransmitters [56]. (2) Genetic mechanisms: The epigenome is a dynamic process, and endogenous mutations in receptor genes may be considered to cause the occurrence of drug-resistant epilepsy [57]. The roles in microbiome are also of great interest in epileptic disorders [58], and earlier research demonstrated that the effects of ketogenic diets for treatment of seizures may be involved in microbial processes [59]. (3) The drug target is missed because most of the anti-epileptic drugs focus on the neuronal inhibition and excitation but do not pay attention to the real pathogenesis caused by encephalitis or cancer. In view of patients with drug-resistant epilepsy, the alternative treatment methods mainly include: (1) surgical treatment via removal of epileptic foci [60], where with the development of epileptic area localization and imaging technology, as well as the in-depth research on the resistance mechanism of epilepsy, comprehensive treatment based on surgery will continue to be improved and promoted, (2) transcranial magnetic stimulation, where the combination of transcranial magnetic stimulation (TMS) and motor cortical EEG enables biomarkers to provide cortical stimulation and suppression measures that are particularly relevant to epilepsy [61], (3) an embedded stimulating electrode, applied to interfere with the synchronization process of abnormal nerve cells’ discharge [62] or for provocation of the electrical current to the vagus nerve [63], and (4) ketogenic diets, which imitate the fasting state by taking in fat as the chief fuel source therapy [64].

4. Cannabinoid System as a Potential Therapeutic Target for Treating Epilepsy

4.1. Endocannabinoid System

The endocannabinoid system (ECS) is involved in regulation of excitatory and inhibitory synaptic transmission in the brain [65,66], and consists of two G protein-coupled receptors, CB$_1$R and CB$_2$R, with two known endogenous cannabinoid ligands, namely 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamide (NAN), respectively [10,11].
In the past few years, scientists have drawn attention to using a treatment focused on ECS [67,68]. There is already a comprehensive review indicating the roles of ECS dysfunction-induced neuroinflammation in epilepsy [69]. Anticonvulsant-like effects of cannabinoid receptor agonists are dependent on CB₁R. CB₁ agonists could increase ATP-sensitive K⁺ channel (K<sub>ATP</sub>) activation by decreasing mitochondrial ATP levels. CB₁R-mediated regulation in neuronal excitability can exert antiseizure effects [70]. Microglia are evoked by pathogens, products of damaged/inflammatory neurons, and destruction of the blood–brain barrier, as well as diverse chemical menace signals. However, there is also a contradiction about suppressing epilepsy by adjusting the activity of CB₁Rs to affect excitability. Owing to the extensive distribution and high level of CB₁ in the CNS under physiological conditions, a risk of side-effects develops when CB₁Rs are activated and targeted.

### 4.2. Cannabinoids’ Effects on Epilepsy

Tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the most researched at present, especially in psychoactive pharmacology. THC and CBD have many similarities in structure, and their structure–activity relationship has an impact on mental activity. It has been reported that both have certain anticonvulsant effects. THC mainly activates the GPR55 receptor, and partially activates the CB₁Rs and CB₂Rs. However, THC can cause a series of psychological effects, such as coordination problems, slower reaction times, memory loss, anxiety, and addiction. CBD can reduce these side-effects caused by THC. Studies have reported that CBD treats the frequency of spontaneous seizures in DS mice mainly by improving the excitability of hippocampal interneurons, and the excitability of vertebral neurons in the dentate gyrus to strong depolarization stimulation is also reduced [67]. The pharmacological activity of CBD is mainly focused on blocking the effect of GPR55 receptors to inhibit the effect of neurotransmission and significantly reduce the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)-mediated amplitude and frequency of induced excitatory postsynaptic currents (EPSCs) and miniature EPSCs (mEPSCs) [71]. CBD is also used clinically to treat epileptic seizures caused by Lennox-Gastaut syndrome [19]. A proportion of patients allocated to CBD treatment in these trials were receiving clobazam (CLB). Bialer and Perucca showed an antiseizure effect of CBD independent of an interaction with CLB. A greater antiseizure effect and greater adverse effects were observed when CBD was combined with CLB [72]. However, the therapeutic effect of CBD on other types of epilepsy and the complete mechanism of action remains unclear, but it may involve a non-CLB mechanism. The peripheral side-effect of CBD is mainly diarrhea. There is only indirect proof implying that CBD could modulate endocannabinoid signaling, but no promising data indicating a direct binding or interaction between CBD and CB receptors. CBD can also partially activate CB₂Rs [73]. Negative allosteric modulation of CB₂R activity by CBD might interpret its action for antiseizure and other neural disorders, which provides us with novel insights to develop its medical application [74]. Regarding CB₂R, CBD-DMH, a modification on different pharmacophoric sties, was considered to promote a conformational change in CB₂R, which favors G protein-dependent signaling rather than β-arrestin-dependent signaling [75]. However, there are very few modulators of CB₁R and CB₂R reported in the literature.

### 4.3. CB₂R Effects on Preclinical Epilepsy

Since CB₂Rs exhibit low expression levels in the brain under normal conditions, but are highly inducible during various disease states (including epilepsy), they appear to be an important substrate for neuroprotection [76]. Targeting CB₂Rs will likely offer a novel therapeutic strategy for treating epileptic seizures without the typical CB₁R-mediated side-effects [77,78]. Emerging evidence has indicated that CB₂Rs are involved in epileptic activity in animal models. In an acute pentylenetetrazol (PTZ) rat seizure model, pretreatment with palmitoyl ethanolamide (PEA) increased the latency of seizure initi-
ation and reduced the duration of seizures, and this antiseizure effect was attenuated by the CB$_2$R antagonist (AM630), suggesting that CB$_2$Rs mediate PEA’s effect [79]. In developing rats, Huizenga et al. examined the antiseizure effects of a variety of cannabinoid ligands, and found that either combined CB$_1$/CB$_2$R or selective CB$_1$R agonists exhibited antiseizure effects in either chemo-convulsing methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate or PTZ seizure models of 10-day postnatal rats [80]. Although the CB$_1$R selective agonist HU-308 did not show an antiseizure effect, the CB$_2$R selective antagonist AM630 did increase seizure severity [80]. In addition, a recent report showed that CB$_1$R knockout (KO) mice did not have an epilepsy phenotype, but co-KO of CB$_1$R and CB$_2$R caused animal epilepsy [81], suggesting that CB$_2$R plays a role in stabilizing the neuronal system. Recent studies have also explored the effects of modulating CB$_2$R activity on seizure susceptibility (Table 1). The activation of CB$_2$Rs decreases excitatory synaptic transmission in the CNS. The new roles for CB$_2$Rs have been identified in inducing hippocampal pyramidal cell hyperpolarization and inhibiting epileptic seizures [12]. The CB$_2$Rs expressed on hippocampal CA3 neurons also play a critical role in reduced neuronal excitation and oscillations [82]. WIN 55212-2, a non-selective CB receptor agonist, shows striking antiseizure effects in a rat epileptic model [83], and CB$_1$R and CB$_2$R double-knockout mice show spontaneous or manual-evoked seizures [81]. CB$_2$R knockout mice including both heterozygous and homozygous exhibit enhanced epileptic susceptibility, and a reduction in CB$_2$R activity is associated with increased susceptibility [84], suggesting that absent CB$_2$Rs can increase seizure susceptibility. The administration of caryophyllene, a CB$_2$R agonist, was found to improve seizure activity in a mouse model [85]. Collectively, these lines of evidence support the idea that the activation of CB$_2$Rs exhibits the antiseizure role. On the other hand, some studies reported different responses by CB$_2$R agonists. For instance, HU-308 [80] and JHW133 [84] show no significant effect on mice seizure occurrence. Moreover, CB$_2$R agonist AM1241 increases seizure intensity in a PTZ model [86]. Additionally, CB$_2$R antagonists AM630 and SR144528 can increase seizure susceptibility [80]. Therefore, it is likely that the altered CB$_2$R activity can affect seizure susceptibility, although the underlying mechanisms are still unclear. The different effects of CB$_2$R-mediated modulations may come from the differences in using different types of CB$_2$R ligands, and be based on different experimental designs, including species, epileptic model types, and dosage. We recently found that the commercially available CB$_2$R agonists showed different effects on pancreatic acinar cell Ca$^{2+}$ oscillations [87]. Nevertheless, numerous lines of evidence have demonstrated that CB$_2$R agonists ameliorate a variety of epileptic seizures, suggesting that CB$_2$R is a potential therapeutic target for treating epilepsy.

### 4.4. CB$_2$R Mediated Anti-Epileptic Effects through a Reduction of Neural Excitability and Synchronization

As a crucial neuro-modulatory system of the brain, the midbrain dopaminergic system plays an important role in neuronal excitability. Temporal lobe epilepsy, involving pathological eterhism of the hippocampus, is associated with VTA dopamine neuron activation [88]. The abnormally high synchronous activity of neuronal firing will cause phased impulse stimulation, causing more dopamine neurons to produce impulse firing, so that the dopaminergic system is in a super-reactive state during seizures’ occurrence [89]. This suggests that the dopaminergic system is vital in epileptic brains, and the evidence for a relationship between epilepsy and the dopaminergic system was previously described by Rezaei [2]. Pilocarpine-induced epileptic rats exhibit a significant enhancement in activity of dopaminergic neurons [88]. In the PTZ kindling model of epilepsy in mice, dopamine neurons within the VTA display hyperactivity when compared to saline-injected controls [90]. Anti-seizure treatments (antiseizure drugs or brain stimulation) are applied to downregulate the neuronal excitability for controlling epileptic seizures.
Table 1. Preclinical evidence for CB₂R-mediated modulations in epilepsy.

| Modulation Approaches | Seizure or Epilepsy Model | Response | References |
|------------------------|---------------------------|----------|------------|
| -                      | PTZ induced seizures in heterozygous and homozygous CB2 knockout mice | Susceptibility | [84] |
| -                      | Handling-induced and spontaneous seizures | Susceptibility | [81] |
| 2-Arachidonoylglycerol (2-AG) | Kainate induced seizures in CB₁R and CB₂R double-knockout mice | Suppressed excitatory | [12] |
| CB₂ agonist beta caryophyllene | PTZ induced seizures in mice | Anticonvulsant activity | [85] |
| CB₂ agonist beta caryophyllene | Induced by kainic acid (KA) seizure in mice | Decreased the seizure scores | [85] |
| CB₂ antagonist AM630 | Kainate induced seizures in CB1R knockout mice | Increased seizure susceptibility | [80] |
| CB₂ agonist AM1241 | PTZ induced seizures in rats | Increased seizure severity | [86] |
| CB₂ agonist HU-308 | DMCM and PTZ induced seizures in rats | No significant effect on seizure severity | [80] |
| CB₂R agonist JWH133 | PTZ induced seizures in mice | No significant effect on seizure severity | [84] |
| CB₂R antagonist SR144528 | PTZ induced seizures in mice | Increases seizure susceptibility | [84] |
| CB1/2R mixed agonist WIN 55,212-2 | DMCM and PTZ induced seizures in rats | Anticonvulsant effects | [80] |

Stimulation of Gₛ-linked G protein-coupled receptors (GPCRs) triggers adenylate cyclase (AC) to produce cAMP from ATP. Activation of this signal pathway causes calcium influx through plasma membrane channels in a calmodulin-dependent manner [91]. Recent studies using transcriptomic analysis show that the transcription of a set of genes related to cAMP signaling is changed in patients suffering from drug-resistant temporal lobe epilepsy [92,93]. When seizures occur, levels of cAMP increase in the brain. The appearance of cAMP signaling can be divided into temporary influence on neuronal excitability, including ion channel or receptor phosphorylation [75], and long-term effects on epileptogenesis, such as effects regulated by cAMP response factor binding protein, CREB [94]. By coupling to Gᵢ proteins, the activation of CB₂Rs causes inhibition of AC activity and downregulation of cAMP release [95]. 5-HA₁A-CB₂ heteroreceptors were characterized in cortical primary cultures of neurons, and 5-HT₁A-CB₂ heteroreceptor complex expression and functionality are significantly enhanced in the brain after cerebral ischemia, especially during the neonatal term, also suggesting that this heteromer is associated with NHIBD pathophysiology [96]. Therefore, CB₂R activation may suppress the occurrence of epilepsy via decreasing excitability of the CNS by reducing the level of cAMP.

Most K+ channels are controlled by various physiological mediators, such as transmembrane voltage, and intracellular Ca²⁺ and G proteins. The roles of K+ in membrane physiology have been extensively investigated in rodent models, and the basic electrophysiological properties and bursting patterns of primate central neurons are generally similar to those reported for the rodent [97]. K⁺ channels are very important in regulating the intrinsic excitability of neurons, and they are the main contributor to neuronal membrane repolarization [98]. K⁺ channels are a promising target for the development of novel anti-epileptic drugs, and activation of the K⁺ channels can be used for restoring control on neuronal excitability in patients with epilepsy [99,100]. Kv7 (M-) channels are an unusual type of K⁺ channel which is different from those that repolarize an individual’s action potential. The M-channels are partially activated within the resting membrane potential of neurons, and further activated by membrane depolarization. The rate of M-channel open and close is slower than other types of K⁺ channels that contribute to the repolarization
of action potentials. Activation of M-channels can inhibit highly synchronized neuronal firing that may reduce hyper-excitation and seizure activity [101]. The K+ channel opener retigabine is a compelling and selective opener of M-type K+ channels and is approved for therapy of drug-resistant focal and focal-to-bilateral tonic-clonic seizures [102]. In VTA DA neurons, G protein-coupled receptor signals regulate the excitability of neurons through a few ion channels, such as G protein-gated internally rectified K+ channels (GIRKs) [50–52]. The CB2R agonist JWH133 has been confirmed to effectively modulate the excitability of neurons by regulating voltage-dependent M-type K+ channels [53].

4.5. Glia CB2R-Mediated Anti-Epileptic Effects via Inflammation and Excitability

More and more lines of evidence show that CB2Rs are relevant to both immune cell competence at the peripheral region [103] and brain cells in the CNS. Actually, neurons, microglia, and astrocytes cells express CB2Rs [32,104,105], which are capable of modulating central neural-immune function and impact the related diseases [106,107]. It is critical to accentuate that CB2R has inducible expression in several immune cells under activated neuroinflammatory conditions. It means that CB2R levels may be upregulated in the CNS and increased in inflamed brain parenchyma due to the invasion of peripheral immune cells (such as peripheral T cells) that express CB2Rs [107]. During activated processes, microglia increase the expression of an array of membrane surfaces of CB2Rs that may be essential in microglial production and/or degeneration within the brain. Both CB1 and CB2 receptors were expressed on microglia using an in vitro assay, including immunoglobulin superfamily receptors, cell component receptors, toll-related receptors, opioid receptors, and cannabinoid receptors [13]. A notable example is that neuropathic pain upregulates CB2Rs in microglia in rat spinal cord, while chronic inflammatory pain does not [108]. When there is an inflammation response in the body, microglia CB2R is rapidly upregulated and activated, which effectively inhibits the release of harmful factors, including TNF-α and free radicals [103].

In patients with epilepsy, medial temporal lobe sclerosis, cortical dysplasia, encephalitis, and glioma, the astrocytes show increased expression of CB2Rs, which may change in K+ currents during seizures. It may lead to overexcitation and changes in a series of enzymatic pathways, which means that astrocytes may change the M-type K+ current by adjusting the expression of CB2Rs to change the intensity of epilepsy. We believe that the role of the astrocyte/astrocytic CB2R–cAMP signaling pathway in controlling epileptogenesis is worthy of further exploration.

5. Conclusions and Perspective

In early studies, CB2Rs were found in the peripheral region, while CB1Rs were mainly expressed in the CNS, which led to a question of the existence of the CB2Rs in the CNS. Nowadays, with the development of more sensitive detection technologies, CB2Rs have been found in multiple brain regions in the CNS, though at a low level of expression compared to CB1Rs. However, CB2R expression and function are rapidly and profoundly increased under pathological conditions in the CNS. This attractive feature means that CB2R is considered as a disease-associated target, suggesting that it will greatly reduce the occurrence of CB1R’s side-effects through modulating the activity of CB2Rs to improve the neurological disorders. Drug-resistant epilepsy seriously affects the quality of life of patients, which highlights the need to invent more effective treatments. Although the underlying mechanisms of drug-resistant epilepsy are still unclear, several novel medicines to improve drug-resistant epilepsy have been developed. One example is the CB1 agonist, THC, which has been replaced by CBD due to its psychoactive side-effect. Epidiolex has been recently approved for the treatment of rare, severe forms of epilepsy by the USA’s Food and Drug Administration (FDA) [109]. Although this shows a promise of targeting the endocannabinoid system as a novel anti-seizure treatment, some harmful side-effects, including somnolence, diarrhea, appetite inhibition, and increased levels of hepatic transaminase [104] and blood pressure [105], limit its use. Considering that CB2Rs
exhibit low expression levels in the brain under normal conditions, but are highly inducible during various disease states (including epilepsy), they appear to be an important substrate for neuroprotection [76]. Targeting CB2Rs will likely offer a novel therapeutic strategy for treating epileptic seizures without the typical CB1R-mediated side-effects [77]. Figure 1 summarizes the potential mechanisms of CB2R activation to inhibit seizures, that include reduced neuronal excitability by downregulating cAMP, and consequently enhanced M-currents in both neurons and astrocytes. In addition, CB2Rs can also regulate immune function and slow down neuroinflammatory responses. Together, it suggests that the CB2R may be an important target for controlling epileptic seizures.

**Figure 1.** Diagram epitomizing the CB2R-associated mechanisms in the modulation of epileptic seizures.

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