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Review

Brain cannabinoid receptor 2: expression, function and modulation

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Abstract

Cannabis sativa (marijuana) is a fibrous flowering plant that produces an abundant variety of molecules, some with psychoactive effects. At least 4% of the world's adult population uses cannabis annually, making it one of the most frequently used illicit drugs in the world. The psychoactive effects of cannabis are mediated primarily through cannabinoid receptor (CBR) subtypes. The prevailing view is that CB_1Rs are mainly expressed in the central neurons, whereas CB_2Rs are predominantly expressed in peripheral immune cells. However, this traditional view has been challenged by emerging strong evidence that shows CB_2Rs are moderately expressed and function in specific brain areas. New evidence has demonstrated that brain CB_2Rs modulate animal drug-seeking behaviors, suggesting that these receptors may exist in brain regions that regulate drug addiction. Recently, we further confirmed that functional CB_2Rs are expressed in mouse ventral tegmental area (VTA) dopamine (DA) neurons and that the activation of VTA CB_2Rs reduces neuronal excitability and cocaine-seeking behavior. In addition, CB_2R-mediated modulation of hippocampal CA3 neuronal excitability and network synchronization has been reported. Here, we briefly summarize recent lines of evidence showing how CB_2Rs modulate function and pathophysiology in the CNS.

Keywords: cannabis; brain cannabinoid receptor 2; GPCR; neuronal excitability; psychiatric disorders; neurological disorders; drug addiction

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Introduction

The cannabinoid type 2 receptor (CB_2R) is a G-protein-coupled receptor that was cloned in 1993[1]. Since then, the expression and function of CB_2Rs in the brain have been debated. Early studies suggested that CB_2Rs were absent in the brain because CB_2 mRNA transcripts were not detected in brain tissue using various methods[2–5]. Based on these findings, CB_2Rs have been considered the "peripheral" cannabinoid receptor[1, 6, 7]. Recently, this concept has been challenged by the identification of CB_2Rs throughout the central nervous system (CNS)[5, 6]. Compared with CB_1Rs, brain CB_2Rs exhibit several unique features: (1) Brain CB_2Rs have lower expression levels than CB_1Rs, suggesting that CB_2Rs may not mediate the effect of cannabis under normal physiological conditions. (2) Brain CB_2Rs are highly inducible; thus, under some pathological conditions (*eg*, addiction, inflammation, anxiety), CB_2R expression is quickly enhanced in the brain[8]. This finding suggests a close relationship between the alteration of CB_2R expression/function and various psychiatric and neurological diseases. (3) Brain CB_2Rs have a specific distribution. Given that they are chiefly expressed in neuronal somatodendritic areas[9] (postsynaptic), the activation of CB_2Rs may lead to opposing effects from CB_1Rs. For example, CB_1Rs are predominantly expressed on neuronal terminals, especially on GABAergic terminals (presynaptic) in ventral tegmental area (VTA) dopamine (DA) neurons[10]. The activation of CB_1Rs reduces GABA release onto DA neurons, leading to an increase in DA neuronal firing through a disinhibition mechanism. However, CB_2Rs are mainly located on postsynaptic somatodendritic areas, and the activation of CB_2Rs reduces VTA DA neuron firing and excitability[11]. Considering these characteristics, CB_2Rs appear to be an important substrate for neuroprotection[12], and targeting CB_2Rs will likely offer a novel therapeutic strategy for treating neuropsychiatric and neurological diseases without typical CB_1R-mediated side effects[13]. Thus, an urgent need to understand the functional effects of CB_2Rs in the brain has emerged.

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Unfortunately, CB_2R-mediated modulation of neuronal functions, including ion channels, receptors, synaptic transmission and plasticity, and neuronal networks in the CNS, has not been well investigated, and to date, studies of the functional effects of CB_2Rs in neurons have ignited debate and controversy due to the following reasons: (1) a lack of highly selective CB_2R antibodies[14]; (2) a lack of full knockout (KO) CB_2R mice as the two types of CB_2R KO mice that have been recently made available are partial knockouts[7]; and (3) under some conditions, CB_1R and CB_2R can form a heteromer[15], which makes the identification of CB_2R function even more complex and difficult. Nevertheless, by combining multiple experimental approaches, several recent papers have described CB_2R expression and function in the brain neurons. Recently, we reported that functional CB_2R was expressed in VTA DA neurons, and activation of VTA CB_2Rs reduces neuronal excitability and cocaine-seeking behavior[11]. It has been reported that CB_2R modulates hippocampal CA1 synaptic plasticity[16] and CA3 neural plasticity and synchronization[17]. In addition, a recent report showed that CB_2R-dependent inhibition of DA release underlies the positive allosteric modulation of the M4 muscarinic receptor in antipsychotic-like effects[18]. These accumulating lines of evidence suggest that brain CB_2Rs are important in the modulation of brain function and disorders.

Brain CB_2R expression

Although early studies were not able to detect CB_2 mRNA transcripts in brain tissue using various methods[2–5], recent lines of evidence show that significant CB_2 mRNA has been detected by *in situ* hybridization (ISH) in the globus pallidus of non-human primates[19]. RT-PCR analysis has also been used to detect CB_2 mRNA expression in various brain regions, including the retina[20], cortex[19, 21–23], striatum[2, 23], hippocampus[17, 19, 24], amygdala[22, 23], brainstem[25], and cerebellum[26]. Furthermore, two CB_2 mRNA transcripts (CB_{2A} and CB_{2B}) are transcribed from two independent promoters in rodent and human tissue[21]. Recently, we have confirmed that CB_2 mRNA is relatively highly expressed in VTA DA neurons[11]. Moreover, immunoblot and immunohistochemical (IHC) assays have detected significant CB_2-like bands or immunostaining in various brain regions[25, 27–30], including the VTA[11]. These findings suggest that CB_2R expression exists not only in peripheral tissue but also in the brain, although the CB_2R expression level in the brain is much lower than that of CB_1R. This low-level brain CB_2R expression suggests that CB_2R may not participate in important brain physiology function; thus, unlike CB_1Rs that mediate serious psychiatric side effects after activation, pharmacological intervention of CB_2Rs has much fewer side effects. In addition to brain neurons, brain glia cells express CB_2Rs[31, 32], where CB_2Rs play an important role in the modulation of central immune function[33] and neuroinflammation-associated diseases[34–36].

Brain CB_2R distribution and function

Although both CB_1Rs and CB_2Rs are G-protein ($G_{i/o}$)-coupled receptors, they exhibit different distributions. In general, the CB_1Rs are mainly expressed in GABAergic neuronal axon terminals, including in VTA GABA neurons[37, 38] and hippocampal CCK-positive GABA neurons[39]. The activation of CB_1Rs reduces presynaptic GABA release, eliminates GABAergic inhibitory control of postsynaptic neurons, and excites these postsynaptic neurons through this dis-inhibition role. However, the CB_2Rs are mainly expressed in the postsynaptic cell body[11, 17]; thus, the activation of these postsynaptic CB_2Rs usually hyperpolarizes the membrane potential and inhibits postsynaptic neuronal function. Therefore, this difference in distribution results in opposite effects after CB_1R and CB_2R activation. Activation of CB_2Rs reduces neuronal excitability through different mechanisms. In VTA DA neurons, activation of CB_2Rs decreases neuronal excitability through the CB_2R-associated modulation of K^+ channel function[11]. In prefrontal cortical neurons, intracellular CB_2Rs are coupled to the G_{q11}-PLC-IP_3 pathway, which opens the Ca^{2+}-dependent Cl^- channels, hyperpolarizes the cell membrane and results in neuronal inhibition[40]. In hippocampal CA3/CA2 pyramidal neurons, activation of CB_2Rs triggers activation of the Na^+/Bicarbonate co-transporter and causes a long-term neuronal hyperpolarization. This CB_2R activation occurs in a purely self-regulatory manner, robustly alters the input/output function of CA3 pyramidal cells, and modulates gamma oscillations *in vivo*[17]. The relatively high expression of CB_2Rs in midbrain DA neurons suggests that they modulate a variety of important DA-associated behaviors[41]. It has been reported that CB_2Rs modulate food intake, body weight[42–45], depression[46], anxiety[22, 47], and schizophrenia-like behavior[23, 48]. Recent reports emerging from several labs, including ours, have shown that brain CB_2Rs play a pivotal role in reducing cocaine, alcohol, and nicotine addiction[49–51]. Collectively, these lines of evidence strongly suggest an important impact of CB_2Rs in the mesocorticolimbic system, as well as critical roles of CB_2Rs in various brain functions, including psychiatric, cognitive, and neurobiological activity.

Inducible feature of brain CB_2Rs and their modulation in neurological and psychiatric disorders

The most attractive property of the CB_2R is its inducible feature. Brain CB_2Rs are expressed at low levels under physiological conditions; however, in pathological conditions, such as neuropathic pain[52], stroke[53], traumatic brain injury[54], neurodegenerative diseases[55–57] or drug addiction[58, 59], CB_2R expression up-regulates quickly and profoundly. This inducible feature lets CB_2Rs serve as a disease-associated target, and pharmacotherapeutic manipulation of CB_2Rs can treat diseases without side effects. For example, the mesocorticolimbic DA system is a key brain circuit implicated in a number of drug addictions. Alterations of the mesocorticolimbic DA circuit are the major cellular mechanisms to promote or prevent drug reward, dependence, and addiction. Emerging evidence has demonstrated that CB_2Rs modulate animal drug-seeking behaviors, including cocaine, alcohol, and nicotine[49–51], suggesting a significant impact of brain CB_2Rs in animal drug reward, dependence, and addiction. Given the

lack of psychoactivity demonstrated by selective CB_2R agonists, CB_2R ligands have been developed as new candidates for the treatment of a variety of neurological and psychiatric disorders[13, 60, 61], including pain[62–65], neuroinflammation[66], stroke[67, 68], Alzheimer's disease[69], Parkinson's disease, and Huntington's disease[36, 70-75]. Three medicines that activate cannabinoid CB_1/CB_2 receptors are now used in clinics: Cesamet (nabilone), Marinol (dronabinol; Δ^9-tetrahydrocannabinol [Δ^9-THC]), and Sativex (Δ^9-THC with cannabidiol). Additionally, a selective CB_2R agonist "Resunab™" has been designated by the FDA for a fast-track development program in a Phase II human clinical trial for scleroderma. However, significant attention is currently being directed at the possibility of developing medicines from compounds that can activate CB_2Rs at doses that induce little or no CB_1R activation. Accumulating lines of evidence have demonstrated that many of the adverse effects induced by mixed CB_1/CB_2 receptor agonists result from CB_1R rather than from CB_2R activation and that CB_2R-selective agonists have a number of important potential therapeutic applications[60]. Therefore, we anticipate the emergence of new drugs that modulate CB_2Rs once a better understanding of the cannabinoid receptors is gained.

Limitation of brain CB_2Rs as a therapeutic target

The major challenge of how to selectively target brain CB_2Rs without affecting peripheral CB_2Rs remains, as CB_2R levels are much higher in peripheral tissues (*eg*, T-cells in the spleen) than in the brain. Thus, systemic exposure of CB_2R ligands to activate brain CB_2Rs will always activate peripheral CB_2Rs. We have two thoughts regarding this challenge: 1) Brain CB_2Rs are dramatically inducible, meaning they are up-regulated during disease conditions such as addiction, degeneration and inflammation. This pathology-associated increase significantly enhances the benefit to side-effect ratio[76]. 2) Activation of brain CB_2Rs protects neurons from pathological conditions (*eg*, addiction, anxiety, stroke, epilepsy, pain) while also activating peripheral CB_2Rs (*eg*, T-cells), which may cause side effects in addition to central therapeutic effects. However, peripheral CB_2R activation will reduce the immune response and prevent an over-inflammatory reaction, which are beneficial for central protective effects. Therefore, the activation of peripheral CB_2Rs may not always induce side effects when brain CB_2Rs are activated, but rather, both central and peripheral CB_2Rs may work together to protect brain neurons from pathological alterations through both neuronal and immune mechanisms. Figure 1 shows a diagram of the impact of brain CB_2R distribution, function and disease.

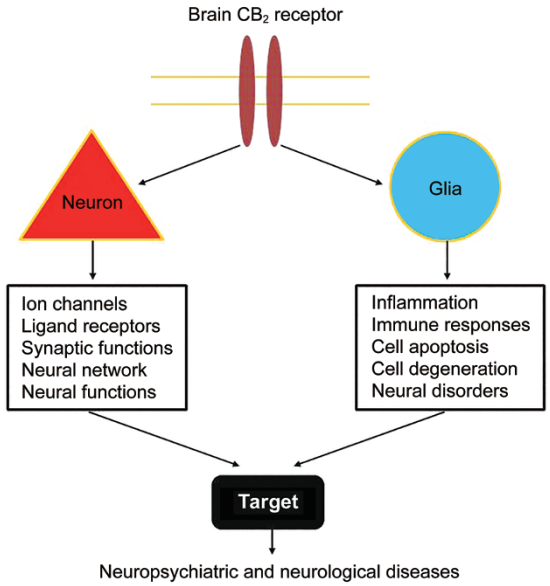

Figure 1. A diagram summarizing brain CB_2R expression and function and the association with neuropsychiatric and neurological diseases. CB_2Rs are expressed in brain neurons, where they participate in the modulation of a variety of neural functions and disorders. CB_2Rs are also expressed in brain glia cells, where they modulate immune function and neuroinflammatory responses. Therefore, brain CB_2Rs are an important target for the modulation of brain function and disease.

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