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Cannabinoids in the descending pain modulatory circuit: Role in inflammation

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Abstract

The legalization of cannabis in some states has intensified interest in the potential for cannabis and its constituents to lead to novel therapeutics for pain, and other disorders. Our understanding of the cellular mechanisms underlying cannabinoid actions in the brain have lagged behind opioids. However, the current opioid epidemic has also increased attention on possible uses of cannabinoids for pain, especially chronic pain that requires long-term use. It is now recognized that endogenous cannabinoids are lipid signaling molecules that have complex roles in modulating neuronal function throughout the brain. In this review, we discuss cannabinoid functions in the descending pain modulatory pathway, and highlight areas where further studies are necessary to understand cannabinoid regulation of descending pain modulation.

Keywords

cannabinoid; endocannabinoid; periaqueductal gray; rostral ventromedial medulla; analgesia; pain; presynaptic terminals

1. Introduction

Intense interest has recently focused on cannabinoids for novel pain therapeutics. Ironically, *Cannabis sativa* (colloquially known as marijuana) has been used for millennia as a medicine for pain and other ailments but its mechanisms of action are not completely understood. With the emerging legalization of cannabis throughout the United States and the world, there is an urgent need for a deeper understanding of the mechanisms underlying cannabinoid effects. Studies of endogenous cannabinoids (endocannabinoids) have begun to elucidate the far-reaching roles of these lipid signaling molecules in modulating neuronal function. In this review, we discuss cannabinoid functions in the descending pain modulatory pathway, and highlight areas where further studies are necessary to understand cannabinoid regulation of descending pain modulation.

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2. Endocannabinoid system

The endocannabinoid system is comprised of the best characterized cannabinoid receptor subtypes 1 (CB1) and 2 (CB2), as well as their natural ligands; termed endocannabinoids (Cristino, Bisogno, & Di Marzo, 2019; Lu & Mackie, 2016). Anandamide (AEA; (Devane, et al., 1992) and 2-Arachidonoylglycerol (2-AG; (Mechoulam, et al., 1995; Sugiura, et al., 1995) are the most well-studied endocannabinoids. These ligands are synthesized "on demand" from membrane lipids in response to cellular signals such as activation of the postsynaptic metabotropic glutamate receptors (mGluRs; (Maejima, Hashimoto, Yoshida, Aiba, & Kano, 2001; Maejima, Ohno-Shosaku, & Kano, 2001; Ohno-Shosaku, Maejima, & Kano, 2001)). AEA and 2-AG are synthesized primarily by N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) and diacyglyerol lipase alpha (DAGLα), respectively. Termination of signaling occurs rapidly through enzymatic degradation by specific lipases. The most thoroughly characterized lipases are monoacyglycerol lipase (MAGL), which degrades 2-AG, and fatty acid amide hydrolase (FAAH) which predominantly degrades AEA (Pertwee, 2015). Each of these components is necessary for maintaining tight control over endocannabinoid levels and their actions on brain circuits.

In addition to these well-characterized endocannabinoids, there are other members that have been shown to modulate pain (Walker, Krey, Chu, & Huang, 2002). Noladin ether, an analog of 2-AG that binds to the CB1 receptor, has similar characteristics to 2-AG but is not found in appreciable quantities in the brain (Oka, et al., 2003), distinguishing it from AEA and 2-AG. N-arachidonoyl dopamine (NADA) is an agonist at both the CB1 receptor and transient receptor potential channel (TRPV1) (Grabiec & Dehghani, 2017) and increases firing of spinal nociceptive neurons in a TRPV1-dependent manner (S. M. Huang & Walker, 2006). Oleoylethanolamine (OEA) is an endocannabinoid-like compound that stimulates the nuclear receptor PPAR-α (peroxisome proliferator-activated receptor alpha) (Laleh, Yaser, & Alireza, 2019) that has been implicated in pain modulation. However, the role of OEA in pain is complex and its pain modulatory effects may be indirect through PPAR-α interacting pathways (Donvito, et al., 2017; Suardiaz, Estivill-Torrus, Goicoechea, Bilbao, & Rodriguez de Fonseca, 2007). A detailed analysis of all of the known endocannabinoids is outside of the scope of this review, but it is worth noting that further understanding of the biosynthesis, regulation and functions of these molecules is no doubt an important step in defining novel targets for pain therapies.

2.1 Cannabinoid receptors

The cannabinoid receptors (CB1 and CB2), as well as a putative cannabinoid receptor GPR55, are seven transmembrane G protein-coupled receptors (GPCRs) that signal predominately through inhibitory $G\alpha_{i/o}$ G proteins. The CB1 receptor was cloned in 1990 (Matsuda, et al., 1990) based on its binding affinity for the natural ligand (delta9-tetrahydrocannabinol, THC) and a synthetic analogue with potent analgesic properties (CP-55,940). This new receptor inhibited forskolin-stimulated adenylyl cyclase activity in a G protein-dependent manner, a hallmark of cannabinoid compounds isolated from cannabis. This opened the door for development of synthetic compounds, both agonists and antagonists, that bind CB1 receptors (Herkenham, et al., 1990). CB1 receptors are the most

abundant GPCRs in the central nervous system (Busquets-Garcia, Bains, & Marsicano, 2018) and are expressed in neurons throughout the central nervous system (Busquets-Garcia, et al., 2018; Herkenham, et al., 1990; Stella, 2010; Turcotte, Blanchet, Laviolette, & Flamand, 2016) where they are primarily expressed in presynaptic terminals and act to inhibit neurotransmitter release (Chevaleyre, Takahashi, & Castillo, 2006; Freund & Hajos, 2003; Freund, Katona, & Piomelli, 2003; Hajos, et al., 2000; S. M. Huang, et al., 2001; Kano, Ohno-Shosaku, Hashimotodani, Uchigashima, & Watanabe, 2009; Katona, et al., 2001; Katona, et al., 1999; Katona, et al., 2006; Mackie, 2005; Morisset & Urban, 2001). More recently, postsynaptic actions of CB1 receptors have been described (Maroso, et al., 2016), but appear to be rare compared to the ubiquitous expression of presynaptic CB1 receptors (for review, see (Busquets-Garcia, et al., 2018).

Historically, CB2 receptors were thought to be expressed exclusively in the periphery, primarily on immune cells, but functional and anatomical evidence now indicates that these receptors are also expressed in the central nervous system (Atwood & Mackie, 2010). CB2 receptor expression has been observed on microglia (Stella, 2010) and is upregulated in inflammation (Maresz, Carrier, Ponomarev, Hillard, & Dittel, 2005). Basally, CB2 receptors are expressed at lower levels compared to CB1 receptors in the midbrain and brainstem (Gong, et al., 2006), although localization studies using putative CB2 receptor antibodies should be interpreted with caution due to issues with specificity (Brownjohn & Ashton, 2012; Cecyre, Thomas, Ptito, Casanova, & Bouchard, 2014; Marchalant, Brownjohn, Bonnet, Kleffmann, & Ashton, 2014). Functional studies using multiple CB2-selective agonists and antagonists provide convincing evidence for CB2-dependent effects in the rostral ventromedial medulla (RVM) (Deng, et al., 2015; M. H. Li, Suchland, & Ingram, 2017) and spinal cord (Beltramo, et al., 2006; Burston, et al., 2013; Guindon & Hohmann, 2008a). Interestingly, CB2 receptor expression appears to be highly dynamic and dependent on the environment as CB2 expression is induced by inflammation and neuropathic pain (Hsieh, et al., 2011; M. H. Li, et al., 2017).

While CB1 and CB2 receptors are the best studied receptors in the cannabinoid system, both endocannabinoids and exogenous cannabinoids can target other receptors. GPR55 is an orphan GPCR that is stimulated by AEA and some lipophilic derivatives of endocannabinoids, as well as AM251 and SR141716A (rimonabant) which are CB1 receptor antagonists (Kapur, et al., 2009; Yang, Zhou, & Lehmann, 2016). GPR55 is expressed on neurons in the dorsal root ganglion (Lauckner, et al., 2008), on adipose tissue (Tuduri, Lopez, Dieguez, Nadal, & Nogueiras, 2017) and microvascular endothelial cells (Leo, et al., 2019) suggesting a wide variety of functions of the endocannabinoid system that are largely unexplored.

Another binding site for AEA is the transient receptor potential channel TRPV1 (Di Marzo, De Petrocellis, Fezza, Ligresti, & Bisogno, 2002). AEA is a full agonist at TRPV1 channels expressed on nociceptive primary afferents, as well as on many central neurons comprising ascending pain circuits. TRPV1 channels are non-selective cation channels gated by capsaicin, protons and heat that promote neuronal excitability. AEA is pro-nociceptive in some situations, promoting responses to painful stimuli (Dinis, et al., 2004) but AEA activation of TRPV1 channels is also antinociceptive, especially in the presence of

inflammation and neuropathic pain (Guindon, Lai, Takacs, Bradshaw, & Hohmann, 2013; Horvath, Kekesi, Nagy, & Benedek, 2008). Taken together, the actions of endocannabinoids depend both on expression of the target receptors on specific cells and on adaptations that are induced in different pain states within specific brain areas.

It should also be noted that there are documented variations in cannabinoid receptor function across species. While the CB1 receptor appears to be well conserved across species with 70% homology between pufferfish and human CB1 receptor amino acid sequence ((Yamaguchi, Macrae, & Brenner, 1996)) and guinea-pig presynaptic CB1 receptor with 98.7% with human CB1 and 99.2% homology with rat or mouse CB1 receptor amino acid sequences (Kurz, Gottschalk, Schlicker, & Kathmann, 2008). The CB2 receptor is not as well conserved across species. CB2 receptor mRNA splicing and expression vary between mice and rats, which impacts CB2 receptor-dependent effects on cocaine self-administration between the species (H. Y. Zhang, et al., 2015). Rat and human CB2 receptors share 81% amino acid homology (Mukherjee, et al., 2004) and profound sequence divergence in the carboxy terminus of mammalian CB2 receptors which could differentially impact receptor regulation including desensitization and internalization (S. M. Brown, Wager-Miller, & Mackie, 2002). Appropriate caution should be employed when comparing CB2 receptor function across species.

2.2 Cannabinoid signaling pathways

Retrograde signaling by endocannabinoids was first described in hippocampal synapses (Maejima, Hashimoto, et al., 2001; R. I. Wilson & Nicoll, 2001). Endocannabinoids are synthesized primarily “on demand” (Ahn, McKinney, & Cravatt, 2008) in response to intense stimulation of afferents impinging on postsynaptic neurons that result in activation of postsynaptic metabotropic glutamate receptors. The endocannabinoids travel retrogradely to impact the presynaptic neuron and inhibit the release of neurotransmitters from presynaptic terminals by binding cannabinoid receptors on the presynaptic terminals (Maejima, Hashimoto, et al., 2001; Maejima, Ohno-Shosaku, et al., 2001; Ohno-Shosaku, et al., 2001; R. I. Wilson & Nicoll, 2001). Transport of endocannabinoids across the membrane into the synapse has been proposed to use facilitated transport (Adermark & Lovinger, 2007) and passive diffusion (Glaser, et al., 2003; Kaczocha, Hermann, Glaser, Bojesen, & Deutsch, 2006) via binding to fatty acid binding proteins (FABPs) (Kaczocha, Glaser, & Deutsch, 2009), or possibly as constituents of extracellular vesicles (Gabrielli, et al., 2015).

Both CB1 and CB2 receptors are inhibitory GPCRs that signal primarily via $G\alpha_{i/o}$ subunits (C. C. Huang, Lo, & Hsu, 2001; Lichtman, Cook, & Martin, 1996), although there is evidence that some cannabinoid receptor agonists stimulate $G\alpha_q$ signaling (Lauckner, Hille, & Mackie, 2005). Cannabinoid agonists inhibit glutamate release in many synapses in the central nervous system, including the prefrontal cortex (Melis, et al., 2004), hippocampus (Misner & Sullivan, 1999), cerebellum (Levenes, Daniel, Soubrie, & Crepel, 1998; Takahashi & Linden, 2000), striatum (C. C. Huang, et al., 2001; Robbe, Alonso, Duchamp, Bockaert, & Manzoni, 2001), and spinal cord (Morisset, Ahluwalia, Nagy, & Urban, 2001; Morisset & Urban, 2001). Cannabinoid agonists also inhibit GABA release in many synapses throughout the brain, including the amygdala (Katona, et al., 2001), cerebellum

(Diana, Levenes, Mackie, & Marty, 2002; Yamasaki, Hashimoto, & Kano, 2006), and nucleus accumbens (Mato, et al., 2004). These lists are by no means exhaustive but illustrate the widespread modulation of neurotransmitter release by the cannabinoid receptors.

CB1 receptors couple to multiple signaling pathways and it appears that each synapse has its own complement of signaling proteins. CB1 receptors effectively couple to several G protein subtypes but efficacy and potency for activation varies widely throughout the brain (Prather, Martin, Breivogel, & Childers, 2000) and is also dependent on the ligand (Diez-Alarcia, et al., 2016). These receptors inhibit presynaptic neurotransmitter release through inhibition of presynaptic Ca^{2+} channels (S. P. Brown, Safo, & Regehr, 2004; C. C. Huang, et al., 2001; Kushmerick, et al., 2004; Mackie & Hille, 1992) and activation of K^+ channels (Daniel, Rancillac, & Crepel, 2004; Robbe, et al., 2001). Endocannabinoids also bind directly to channels to modulate their gating and/or ion flux, including A-type potassium channels, TRPV1, $GABA_A$, nicotinic acetylcholine, glycine and HCN channels (Gantz & Bean, 2017; Maroso, et al., 2016; Oz, Ravindran, Diaz-Ruiz, Zhang, & Morales, 2003; Sigel, et al., 2011; Xiong, et al., 2012; Zygmunt, et al., 1999). The multiple cellular mechanisms underlying CB1 receptor inhibition of neurotransmitter release may contribute to the difficulty in targeting CB1 receptors for novel therapeutics because the signaling pathways are different in individual synapses, even within specific brain areas.

2.3 Regulation of synaptic plasticity

Endocannabinoids can produce both short-term, transient inhibition of neurotransmitter release (Diana & Marty, 2004; Kreitzer & Regehr, 2002; R. I. Wilson & Nicoll, 2002) and longer, more sustained inhibition (Chevaleyre & Castillo, 2003; Chevaleyre, et al., 2006; Gerdeman & Lovinger, 2003; Gerdeman, Ronesi, & Lovinger, 2002; Robbe, Kopf, Remaury, Bockaert, & Manzoni, 2002; Ronesi, Gerdeman, & Lovinger, 2004; Sjostrom, Turrigiano, & Nelson, 2003; Yin, Davis, Ronesi, & Lovinger, 2006). Depolarization-induced suppression of excitatory (DSE) or inhibitory (DSI) transmission are examples of short-term plasticity that last during stimulation or shortly after stimulation is terminated. In these experiments, the postsynaptic cell is depolarized, allowing for calcium entry, synthesis of endocannabinoid ligands and retrograde transport of the endocannabinoids to presynaptic terminals to bind presynaptic CB1 receptors. Interestingly, not all synapses display DSE/DSI (Hentges, Low, & Williams, 2005; Kreitzer & Malenka, 2005) suggesting that depolarization is not required for endocannabinoid synthesis and release at all sites. Indeed, GPCRs coupled to $G\alpha_q$, for example Group I metabotropic glutamate receptors and muscarinic receptors, appear to be sufficient (Kreitzer & Malenka, 2005; L. A. Martin & Alger, 1999; Morishita, Kirov, & Alger, 1998). Endocannabinoids have also been implicated in short-term depression (STD) via metabotropic glutamate receptor activation of phospholipase C (Sternweis, Smrcka, & Gutowski, 1992), as well as long-term depression (LTD) at both glutamatergic and GABAergic synapses. These forms of endocannabinoid-induced plasticity are carefully reviewed in ((Lovinger, 2008).

2.4 Role of cannabinoids in inflammation

Cannabinoids have an important role in regulating inflammatory processes in the periphery. Many studies, both *in vitro* and *in vivo*, have shown that CB1 and CB2 receptor agonists, as

well as FAAH and MAGL inhibitors, inhibit the development and maintenance of inflammation (for reviews, see (Donvito, et al., 2018; Guindon & Hohmann, 2009). Both cannabinoid receptors inhibit edema associated with carrageenan and CFA injections into rodent paws, and regulate the release of pro-inflammatory and anti-inflammatory cytokines (Cabral & Griffin-Thomas, 2009). Although these peripheral effects of cannabinoids are important in the overall response to systemic administration of cannabinoid receptor agonists and other drugs that modulate the endocannabinoid system in inflammation, this review will focus on the role of cannabinoids in the descending pain modulatory circuit in the brain.

3. Descending pain modulatory system

The descending pain modulatory circuit is comprised of the ventrolateral periaqueductal gray (PAG) projections to the rostral ventromedial medulla (RVM) and their reciprocal connections with upstream cortical and subcortical brain areas and downstream spinal cord neurons, respectively. Activation of this system typically results in analgesia (Barbaro, 1988; Castillo, Younts, Chavez, & Hashimotodani, 2012; Daniel, et al., 2004; Di Marzo, Blumberg, & Szallasi, 2002; Di Marzo & De Petrocellis, 2010; Fardin, Oliveras, & Besson, 1984; M. M. Heinricher & Ingram, 2008; Hosobuchi, 1980; Kano, et al., 2009; Mayer, 1984; Morishita, et al., 1998; M. Silva, et al., 2016; Starowicz, et al., 2013; Starowicz, et al., 2012; Stella, 2010). However, this circuit is subject to plasticity during pain states, and prolonged pain results in a switch in the output from the RVM from inhibition of pain to facilitation of pain (Burgess, et al., 2002; Carlson, Maire, Martenson, & Heinricher, 2007; Cleary & Heinricher, 2013; Kincaid, Neubert, Xu, Kim, & Heinricher, 2006; Roberts, Ossipov, & Porreca, 2009; W. Zhang, et al., 2009) indicating that the circuit is bi-directional in terms of pain modulation (Carlson, et al., 2007; Cleary & Heinricher, 2013). Both the PAG and RVM integrate information from higher brain centers that contribute brain processing of emotional and cognitive aspects of pain prior to regulating pain thresholds at the level of the spinal cord. Emotional aspects of pain are critical in the individual experience of chronic pain and thus, it is critical that cannabinoid actions within this circuit are well understood.

3.1 Inputs and outputs of the descending pain modulatory pathway

The vlPAG is an integration center for the descending pain modulatory pathway, receiving inputs from a variety of cortical and subcortical brain regions, as well as from the spinal cord (M. M. Heinricher & Ingram, 2008; Keay & Bandler, 2001; C. Silva & McNaughton, 2019). The vlPAG receives inputs from regions that are targets of the ascending nociceptive fibers, including the parabrachial area and spinal cord, as well as regions associated with affective aspects of pain including the ventral tegmental area (VTA) (Breton, et al., 2019), prefrontal cortex (Floyd, Price, Ferry, Keay, & Bandler, 2000), hypothalmus (Keay & Bandler, 2001) and amygdala (Hopkins & Holstege, 1978; J. N. Li & Sheets, 2018).

Efferents of the vlPAG project to many brain regions including the VTA and substantia nigra (C. Silva & McNaughton, 2019; Suckow, Deichsel, Ingram, Morgan, & Aicher, 2013), but pertinent to this review is the dense projection to the RVM. The RVM also receives nociceptive transmission from the parabrachial complex (Q. Chen, et al., 2017). The RVM

sends a dense projection to the dorsal horn of the spinal cord (Francois, et al., 2017), as well as the trigeminal nucleus (Aicher, Hermes, Whittier, & Hegarty, 2012). While the PAG and RVM are involved in multiple processes, their role in descending modulation of pain is well documented (M. M. Heinricher, 2016) and is the main focus of these regions in this review.

3.2 PAG

The PAG is a heterogeneous cell dense structure organized in columns running in the rostral-caudal axis surrounding the cerebral aqueduct. The columns serve different functions: stimulation of the ventrolateral column produces opioid-mediated analgesia, as well as freezing and quiescent behaviors, whereas stimulation of the lateral column and more dorsal columns produce escape behaviors such as jumping and flight responses (Keay & Bandler, 2001). Detailed analysis of the columns within the PAG is outside of the scope of this review, but has recently been reviewed (C. Silva & McNaughton, 2019).

PAG output neurons to the RVM are inhibited by GABA under normal conditions. Removal of this inhibition, termed *disinhibition*, results in activation of the descending pain modulatory circuit and analgesia (reviewed in (M. M. Heinricher & Ingram, 2008; Lau & Vaughan, 2014). The assumption is that disinhibition promotes excitatory neurotransmission from the PAG to RVM; however, opioid receptors are expressed on both GABAergic and glutamatergic terminals in the PAG and both cell populations project to RVM (M. M. Morgan, Whittier, Hegarty, & Aicher, 2008). Thus, PAG to RVM circuitry is more complicated than simply disinhibition of excitatory descending projections and probably reflect the existence of parallel circuits that contribute to the bidirectional control of pain mediated by the RVM.

The PAG also contains circuits that respond to threatening and stressful stimuli, as well as homeostatic control of feeding, lactation and respiration (Silva, et al., 2019). Many of these PAG circuits, in addition to the pain modulatory circuits, are sexually dimorphic (Loyd, Morgan, & Murphy, 2007; Loyd & Murphy, 2006; Loyd, Wang, & Murphy, 2008) whereby activation of the PAG results in differential responses in males and females. The reasons for these differences probably reflect environmental, as well as biological factors. We recently observed that GABA release was increased selectively in females in the presence of inflammation (Tonsfeldt, et al., 2016). Because modulation of GABA release is important for activation of the descending pain modulatory circuit, adaptations contributing to increases in GABA release could elucidate cellular mechanisms leading to chronic pain.

3.3 RVM

The RVM receives a dense input from the PAG, as well as afferents from the hypothalamus, parabrachial nucleus, and a variety of other cortical and subcortical areas (M. M. Heinricher & Ingram, 2008). This area provides the main output from the descending pain modulatory circuit to the spinal cord (Fields, Malick, & Burstein, 1995; M. M. Heinricher, Tavares, Leith, & Lumb, 2009). The RVM contains two types of neurons that respond to noxious stimuli; OFF-cells stop firing and ON-cells fire just prior to the behavioral response to a noxious stimulus. ON-cell firing promotes hyperalgesia (M. M. Heinricher & Neubert, 2004; Neubert, Kincaid, & Heinricher, 2004). Opioids, but not cannabinoids, directly

hyperpolarize RVM ON-cells (Vaughan, McGregor, & Christie, 1999). ON-cells in the RVM express the mu opioid receptor (Barbaro, Heinricher, & Fields, 1986; M. M. Heinricher, Morgan, & Fields, 1992) and it has become widely accepted that mu opioid receptor agonist sensitivity defines this cell population (Phillips, et al., 2012; Porreca, et al., 2001). RVM OFF-cells pause firing in response to a nociceptive stimulus and just prior to the behavioral withdrawal from the stimulus (Fields, Bry, Hentall, & Zorman, 1983). Opioids and cannabinoids reduce the pause response from these cells and prolong the latency to withdraw from the stimulus (i.e., antinociception, (M.M. Heinricher, Morgan, Tortorici, & Fields, 1994; Meng & Johansen, 2004; Meng, Manning, Martin, & Fields, 1998). The drugs elicit firing of OFF-cells by reducing GABAergic inputs to the cells. Interestingly, if OFF-cells are firing and do not pause, the behavioral output is analgesia, regardless of the activity of ON-cells. This fairly simple classification of neurons in the RVM is an interesting comparison to the heterogeneous PAG. While 'ON' and 'OFF' cells have been identified in the PAG *in vivo* (M. M. Heinricher, Z. F. Cheng, & H. L. Fields, 1987), PAG neurons are fairly "quiet" with few basally active neurons and a low percentage of neurons that respond to noxious stimuli (M. M. Heinricher, Z.-F. Cheng, & H. L. Fields, 1987; Tryon, Mizumori, & Morgan, 2016).

3.4 Cannabinoids in pain

Although cannabis, has been used for centuries to relieve pain, the cloning of cannabinoid receptors and identification of an endogenous cannabinoid has lagged behind similar advances in the opiate system. The effects of opioids in the descending pain modulatory system have been studied in detail and reviewed previously (Heinricher & Ingram, 2008; Lau & Vaughan, 2014). In contrast to opioids, much less is known about cannabinoid regulation of this circuit. Early studies from the Hargreaves laboratory discovered that intrathecal administration of a CB1 antagonist SR 141716A produced hyperalgesia (increased pain sensitivity) when measuring thermal hot plate latencies in mice (J. D. Richardson, Aanonsen, & Hargreaves, 1997; J.D. Richardson, Aanonsen, & Hargreaves, 1998). These studies documented that endocannabinoids are tonically released, at least in some areas of the CNS, and regulate thermal nociceptive thresholds. The tonic release of endocannabinoids under normal conditions is in stark contrast to the opioid system which is engaged following stress or threatening situations (Walker, Huang, Strangman, Tsou, & Sanudo-Pena, 1999). Although it is clear that cannabinoids are not as efficacious as opioids in reducing acute pain when administered directly into the PAG or RVM (W. J. Martin, Tsou, & Walker, 1998), they appear to have increased efficacy in chronic pain states (Donvito, et al., 2018; Woodhams, Chapman, Finn, Hohmann, & Neugebauer, 2017). Clinically, the use of chronic opioids lacks efficacy for the treatment of chronic pain (Krebs, et al., 2018) while there is demonstrable efficacy of cannabinoids for chronic pain relief (Whiting, et al., 2015, (Cousijn, Nunez, & Filbey, 2018; Whiting, et al., 2015).

4. Mechanisms of cannabinoid action in the descending pain modulatory pathway

4.1 Cannabinoid signaling in the PAG

The PAG is an important region for the antinociceptive effects of cannabinoids (Lichtman, et al., 1996). Behavioral studies indicate that direct injection of cannabinoid agonists into the PAG produces mild hypoalgesia that is approximately 1/3 of an equi-potent dose of morphine (Palazzo, et al., 2001; Wilson-Poe, Pocius, Herschbach, & Morgan, 2013). PAG microinjections of cannabinoids also reduce hyperalgesia induced by formalin (de Novellis, et al., 2005; Finn, et al., 2003). These studies provided evidence that CB1 receptors in the PAG can activate the descending pain modulatory circuit and have efficacy at inhibiting inflammatory pain.

The CB1 receptor is highly expressed throughout both the dorsolateral and ventrolateral periaqueductal gray (Wilson-Poe, Morgan, Aicher, & Hegarty, 2012) and extend throughout the rostral and caudal PAG (Tsou, Brown, Sanudo-Pena, Mackie, & Walker, 1998). Activation of CB1 receptors in the vlPAG produce antinociception and anti-hyperalgesia (Palazzo, et al., 2012) and have actions similar to opioids. CB1 receptors in the dorsal lateral PAG mediate opioid-independent stress-induced analgesia (Hohmann, et al., 2005).

Similar to the mu opioid receptor, cannabinoid receptors are expressed on both GABAergic and glutamatergic terminals within the lateral and ventrolateral PAG (Vaughan, Connor, Bagley, & Christie, 2000) and inhibit the release of both neurotransmitters (Vaughan, et al., 2000) (Figure 1). Immunohistochemical evidence indicates that CB1 receptors may be expressed abundantly (50%) on the postsynaptic membrane within the PAG (Wilson-Poe, et al., 2012), although electrophysiological studies have found no evidence of postsynaptic function of the CB1 receptors (Vaughan, et al., 2000). The function of these putative postsynaptic CB1 receptors is not known so they either couple to signaling pathways that do not alter electrophysiological properties of the neurons or they represent an artifact of antibody staining in the rat. Thus far, there is no evidence of CB2 receptor activity within the PAG under normal conditions (unpublished observations).

The signaling pathways involved in CB1-mediated inhibition of neurotransmitter release in the PAG is not currently known. CB1 receptor-mediated inhibition of GABA release in the ventrolateral PAG is not affected in the presence of nominal concentrations of Ca^{2+} and cannabinoid agonists do not block voltage-gated Ca^{2+} channels in isolated PAG neurons (Vaughan, et al., 2000). In addition, db-cAMP microinjections into the PAG do not reverse the analgesia produced by a CB1 receptor agonist (Lichtman, et al., 1996) indicating that CB1 receptors are not eliciting analgesia via inhibition of adenylyl cyclase. Another possibility is that CB1 receptors couple to phospholipase A2 and voltage-gated potassium channels in presynaptic terminals, since mu opioid receptors act on this pathway in the PAG. Preliminary experiments show that alpha-dendrotoxin, an inhibitor of voltage-gated potassium channels diminish, but does not abolish, the effects of the cannabinoid agonist WIN55212 (Ingram lab, unpublished observations). However, there is a lack of cross-tolerance between cannabinoids and opioids (Vigano, et al., 2005; A. R. Wilson, Maher, &

Morgan, 2008) suggesting that these two receptors likely use non-overlapping signaling pathways. Thus, the signaling pathway for CB1 receptors on presynaptic terminals in the PAG has not been characterized to date.

CB1 receptor signaling regulates different modes of release from presynaptic terminals. First, they can reduce the probability of release, similar to effects of opioids (Drew, Lau, & Vaughan, 2009; Drew, Mitchell, & Vaughan, 2008; Vaughan, et al., 2000). Second, GABA release in the PAG is often multi-vesicular and endocannabinoids disrupt this mode of release, shifting the balance toward univesicular release (Aubrey, Drew, Jeong, Lau, & Vaughan, 2017). It is thought that the multivesicular release from GABAergic terminals in the vlPAG is critical for normal suppression of the descending analgesic circuit so that tight regulation of release mode by endocannabinoids allows for rapid responses to pain or stress.

Under stress or pain stimuli, enhanced release of glutamate activates metabotropic glutamate receptors that stimulate production of endocannabinoids in the PAG (Drew, et al., 2009; Drew, et al., 2008; Drew & Vaughan, 2004). Endocannabinoid synthesis is also stimulated by muscarinic activation of M1 receptors (Lau and Vaughan 2008), as well as several neuropeptides (Substance P, neurotensin, CCK) that induce glutamate release in the PAG (Drew, et al., 2009; Drew, Mitchell, & Vaughan, 2005; Mitchell, Jeong, Drew, & Vaughan, 2011; Mitchell, Kawahara, & Vaughan, 2009). Activation of all of these GPCRs leads to retrograde inhibition of neurotransmitter release in the PAG. Increased endocannabinoid release has also been detected after chronic constriction injury (Petrosino, et al., 2007) and formalin injections (Walker, et al., 1999). Further, blockade of endocannabinoid hydrolysis by FAAH in the PAG produces antinociception (Maione, et al., 2006) and enhances stress-induced analgesia (Hohmann, et al., 2005; Suplita, Farthing, Gutierrez, & Hohmann, 2005). Thus, endocannabinoid actions in the PAG are stimulated by multiple neurotransmitters and neuropeptides that are linked to modulation of nociceptive thresholds.

GPR55, the orphan cannabinoid receptor, has a controversial role in antinociception. GPR55 knock-out mice display decreased mechanical hyperalgesia in inflammatory and neuropathic pain models (Staton, et al., 2008) but no detectable differences in the development of pathological pain in chemical and neuropathic pain models were observed in another study (Carey, et al., 2017). GPR55 agonists reduce nociceptive thresholds when microinjected into the PAG (Deliu, et al., 2015) suggesting that other endocannabinoid agonists of GPR55 may have actions in the PAG. These results indicate that studies of cannabinoid regulation of pain need to be interpreted with caution and use appropriate controls to rule out potential actions at GPR55.

4.2 Cannabinoid signaling in the RVM

In the RVM, acute inflammation or injury is associated with sustained activation of ON-cells and suppression of OFF-cell firing, leading to hyperalgesia (Cleary & Heinricher, 2013; Kincaid, et al., 2006; Xu, Kim, Neubert, & Heinricher, 2007). Lidocaine injections into the RVM inhibit ON-cell firing and hyperalgesia (Kincaid, et al., 2006) indicating that the RVM provides a pro-nociceptive output to the spinal cord under these conditions. In contrast, in chronic pain models, ON- and OFF-cells in the RVM exhibit profoundly lowered thresholds, responding to innocuous as well as noxious peripheral stimulation (Carlson, et al., 2007;

Cleary & Heinricher, 2013). In addition, lidocaine block within the RVM under these conditions worsen hyperalgesia (Cleary & Heinricher, 2013) indicating that output from the RVM is antinociceptive. These changes in the properties of RVM pain-modulating neurons likely reflect a combination of altered afferent input, intrinsic properties, and synaptic plasticity in the transition from acute to chronic pain.

Cannabinoids microinjected into RVM also produce a modest analgesic effect (W. J. Martin, et al., 1998) and can potentiate the analgesic response to a low dose of opioid (Wilson-Poe, et al., 2013). *In vivo* recordings indicate that CB1 receptor agonists activate RVM OFF-cells (Meng & Johansen, 2004; Meng, et al., 1998), consistent with their effects on behavior. In *ex vivo* slice recordings, CB1 receptor agonists inhibit GABA release in the RVM (M. H. Li, Suchland, & Ingram, 2015; Vaughan, et al., 1999) but it is not known if glutamate release in the RVM is inhibited by cannabinoids. It is also not currently known what role endocannabinoids play in the transition from antinociception to hyperalgesia after prolonged pain, although inflammation alters expression of CB1 receptors in the RVM (M. H. Li, et al., 2017) which will be discussed in more detail below. Given that this area is the key output node of the descending pain modulatory system, continued study of cannabinoid signaling in the RVM is important.

An interesting side note is that tonic endocannabinoid signaling is only observed in adult RVM slices but not in early postnatal rats, indicating that the endocannabinoid system is developmentally regulated in this area (Kwok, et al., 2017; M. H. Li, et al., 2015). Thus, the cannabinoid system is developing, at least in some brain areas, during adolescence which potentially has important clinical implications considering the increasing prevalence of cannabis use in adolescents.

4.3 Phytocannabinoids in the descending pain modulatory pathway

Phytocannabinoids, or the cannabinoids derived from the plant *Cannabis sativa*, have different properties than synthetic cannabinoids such as WIN 55,212–2 or CP 55,940 that are used in the majority of the animal studies cited throughout this review. Cannabidiol (CBD) is thought to impart the majority of the pain-relieving benefits of cannabis despite the fact that it does not have efficacy at either CB1 or CB2 receptors (REF). The effects of CBD on the descending pain modulatory pathway are largely unknown. CBD microinjectionsinto the vlPAG decreased both RVM ON- and OFF-cell activity (Maione, et al., 2011) and produced antinociceptive effects. However, these results are not consistent with known actions of antinociceptive drugs on RVM neurons (M.M. Heinricher, et al., 1994). In addition, CBD produces anti-anxiogenic actuions in the PAG that are probably mediated via 5HT1A receptors (Campos & Guimaraes, 2008; Moreira, et al., 2009).

5. Synaptic plasticity with inflammation

Studies examining the analgesic actions of both opioids and cannabinoids in the descending pain modulatory circuit have largely focused on regulation of GABA release and $GABA_A$ receptors in the PAG and RVM. Blocking $GABA_A$ receptors in either the PAG or RVM elicits antinociception (Bobeck, McNeal, & Morgan, 2009; Gilbert & Franklin, 2001; Moreau & Fields, 1986; Tortorici & Vanegas, 1994). In addition, chronic inflammation and

neuropathic pain modulate GABA release in these areas, although both increases and decreases in GABA release have been reported (T. Chen, et al., 2013; Hahm, Kim, Lee, & Cho, 2011; M. H. Li, et al., 2017; Y. Zhang, et al., 2011) indicating the complexity of the compensatory changes in the descending pain circuit. Indeed, regulation of GABA in the PAG during chronic inflammation is also sex-dependent (Tonsfeldt, et al., 2016).

Cannabinoid receptors in the descending pain modulatory pathway are plastic as their expression and function changes in response to various manipulations, including persistent inflammation. We recently documented this plasticity in the RVM following CFA injections into the hind paw of rats and the development of persistent inflammation lasting 5–7 days (Figure 2). We observed a decrease in CB1 receptor-mediated inhibition of GABA release in the RVM of CFA-treated rats (M. H. Li, et al., 2017). Although there is evidence that CB1 receptors desensitize in response to exogenous cannabinoid administration (Lazenka, et al., 2014; Mikasova, Groc, Choquet, & Manzoni, 2008; D. J. Morgan, et al., 2014; Selley, Cassidy, Martin, & Sim-Selley, 2004) and upregulation of endocannabinoids (Imperatore, et al., 2015; Navia-Paldanius, et al., 2015), However, we measured down-regulation of CB1 receptors without a change in CB1 mRNA in the RVM (M. H. Li, et al., 2017) indicating that CB1 receptor translation or degradation are modulated by inflammation. We also observed a decrease in CB1 receptor-mediated inhibition of GABA release in the PAG but have not examined CB1 receptor mRNA or protein to date (Ingram lab, unpublished observations). These results are consistent with observed down-regulation of CB1 receptor protein (but not mRNA) in the PAG following the chronic constriction injury model of neuropathic pain (Palazzo, et al., 2012). CB1 receptor down-regulation has also been observed following repeated exposure to cannabinoids (Breivogel, et al., 1999; Dudok, et al., 2015; Sim, Hampson, Deadwyler, & Childers, 1996). Taken together, these data indicate that drugs that selectively target CB1 receptors may not be clinically useful in some types of inflammatory and neuropathic pain. Conversely, cannabinoid agonists that bind to CB2 receptors may be beneficial for the treatment of inflammatory and neuropathic pain. Consistent with previous findings, CB2 receptors in the RVM were upregulated in persistent inflammation, and CB2 receptor agonists inhibited presynaptic GABA release in the RVM of CFA-treated rats but not naïve rats (M. H. Li, et al., 2017). It is interesting that these receptors are upregulated and appear to function in a manner comparable to that of CB1 receptors in the region. However, there are many aspects of the CB2 receptor actions in the RVM that are not understood. For instance, it is not known what signals trigger CB2 receptor expression nor it is known where the CB2 receptors are localized. Low levels of mRNA and inadequate CB2 receptor antibodies have not allowed visualization of these receptors and we have been reliant on pharmacological data examining the function of a myriad CB2 receptor ligands. However, other studies also find evidence for upregulation of cannabinoid receptors during inflammation (Beltramo, et al., 2006; Burston, et al., 2013). There are also studies that support the idea that CB2 receptors are relevant targets for chronic pain therapeutics for inflammatory (Beltramo, et al., 2006; Burston, et al., 2013; Deng, et al., 2015; Guindon & Hohmann, 2008a) and neuropathic (Guindon & Hohmann, 2008a; Ibrahim, et al., 2003; Sagar, et al., 2005; J. Zhang, et al., 2003) pain.

6. Clinical implications

Endocannabinoids and cannabinoid receptors are clearly situated to modulate processing of pain from peripheral stimulation of nociceptive afferents to central circuits involved in the emotional and cognitive aspects of the pain response. The ubiquitous expression of CB1 receptors and the enzymes that regulate endocannabinoid synthesis and degradation throughout the brain probably limits the therapeutic potential of pharmacological drugs that target these proteins exclusively. Another issue is that the endocannabinoids inhibit release of both glutamate and GABA, so it is difficult to predict how the drugs would alter any specific circuit. While there is little evidence of clinically-relevant acute or experimental analgesia in humans, there an ever-growing literature documenting evidence of pain management with cannabis and cannabinoids (Cousijn, et al., 2018; Hill, 2015). The clinical data has been elegantly reviewed recently (Lotsch, Weyer-Menkhoff, & Tegeder, 2018; Woodhams, et al., 2017) and will not be reviewed in detail here. Interestingly, studies predominately observe weak to no analgesic effects of cannabinoid agonists even though cannabinoids decrease functional connectivity of the “pain matrix” in functional magnetic resonance (fMRI) studies (Walter, et al., 2016). However, it should be noted that many of the fMRI studies have examined pain responses in healthy subjects to date, not subjects in chronic pain. The incongruency between pain relief in clinical studies and lack of reliable antinociception produced by cannabinoids emphasizes the multifaceted aspects of pain and that analgesia is only one aspect of clinical pain relief. Meta-analyses of clinical chronic pain studies show that the modest effects of cannabinoids may be a result of effects of cannabinoids on sleep and mood (Andreae, et al., 2015; Sharon & Brill, 2019; Walitt, Klose, Fitzcharles, Phillips, & Hauser, 2016; Yanes, et al., 2019). All studies conclude that more double-blind, placebo-controlled research is needed to understand the utility of cannabinoid therapies for pain.

One interesting strategy is to use cannabinoid therapies in conjunction with other analgesics, such as NSAIDs or opioids. There is a substantial preclinical literature on synergistic analgesia produced by FAAH inhibitors with morphine or other opioids (Casey, Atwal, & Vaughan, 2017; Christie, Vaughan, & Ingram, 1999; Kazantzis, Casey, Seow, Mitchell, & Vaughan, 2016) for neuropathic pain. A clinical trial using a FAAH inhibitor for osteoarthritis in the knee found no significant benefit (Huggins, Smart, Langman, Taylor, & Young, 2012) but a recent study found that a patient with a FAAH mutation presented with higher anandamide levels and insensitivity to pain (Habib, et al., 2019). CB2 receptor agonists are also synergistic with morphine in in rodent models of acute and chronic inflammatory, post-operative, and neuropathic pain (Grenald, et al., 2017). These studies suggest that lower doses of opioids, when used in combination with cannabinoid agonists, can be used to effectively treat pain, decreasing frequency of opioid-induced side-effects. Indeed, chronic pain patients reliably reduce their opioid consumption by 40–50% when using adjunct cannabis (Boehnke, Litinas, & Clauw, 2016; Gruber, et al., 2016; Haroutounian, et al., 2016; Reiman, Welty, & Solomon, 2017). The opioid-sparing effects alone may support the use of cannabinoid-based therapies. However, long-term clinical use of cannabinoid therapies are at the early stage of investigation and more clinical trials are necessary to fully evaluate the efficacy of this class of drugs.

7. Conclusions

While cannabis has been used over the years for pain relief, the mechanisms of action are not fully understood. Cannabinoid receptors and the enzymes that synthesize and degrade endocannabinoids are highly expressed throughout the descending pain modulatory pathway and further study of their functions in this circuit are likely to lead to a better understanding of the physiology underlying processing of pain, as well as elucidating better pain therapeutics. The fact that the overwhelming public perception is that cannabinoids are effective for pain, in addition to the recent rapid changes in legalization of cannabis and its constituents throughout the United States, as well as other countries, highlights the need for further study of endocannabinoids, their role in modulating pain circuits and plasticity in different chronic pain states.

Abbreviations

2-AG	arachidonolyglyerol
AA	arachidonic acid
AEA	anandamide
CB1	cannabinoid receptor subtype 1
CB2	cannabinoid receptor subtype 2
CFA	Complete Freund’s adjuvant
DSE	depolarization-induced suppression of excitatory neurotransmission
DSI	depolarization-induced suppression of inhibitory neurotransmission
FAAH	fatty acid amide hydrolase
GPCR	G protein-coupled receptor
MAGL	monoacylglycerolipase
PAG	periaqueductal gray
RVM	rostral ventromedial medulla
TRPV1	transient receptor potential cation channel subfamily V member 1

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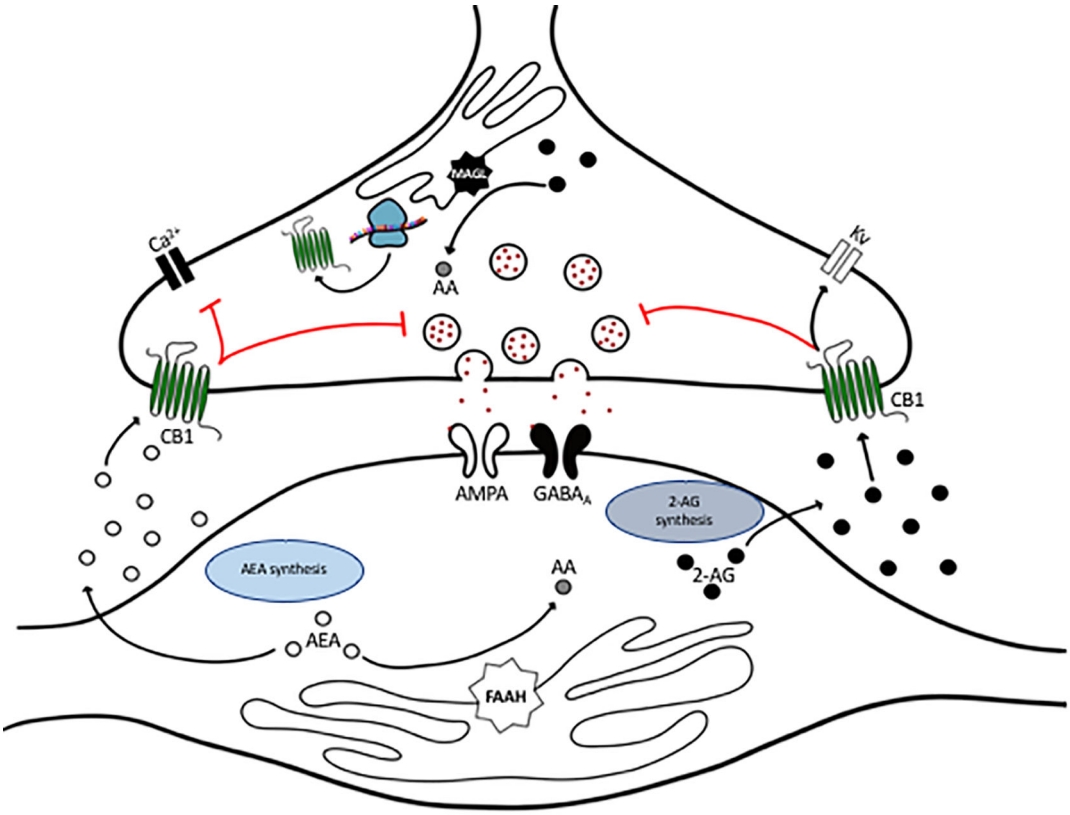

Figure 1.

Schematic of the CB1 receptor-mediated inhibition of presynaptic neurotransmitter (glutamate and GABA) release. The endocannabinoids anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) are synthesized in response to stimulation of postsynaptic cells. They diffuse through the membrane or are transported across the membrane to act at cannabinoid subtype 1 (CB1) receptors expressed on presynaptic terminals. CB1 receptors are translated in the presynaptic terminals in a mTOR-dependent manner in some synapses. Activation of CB1 receptors inhibit release via several signaling cascades, including activation of voltage-gated potassium channels (Kv), inhibition of Ca^{2+} channels and direct inhibition of vesicle release machinery. Termination of signaling occurs through enzymatic breakdown. Monoacyglycerol lipase (MAGL) is expressed in the presynaptic terminal and degrades 2-AG while fatty acid amide hydrolase (FAAH), which predominantly degrades AEA, is localized to postsynaptic cells.

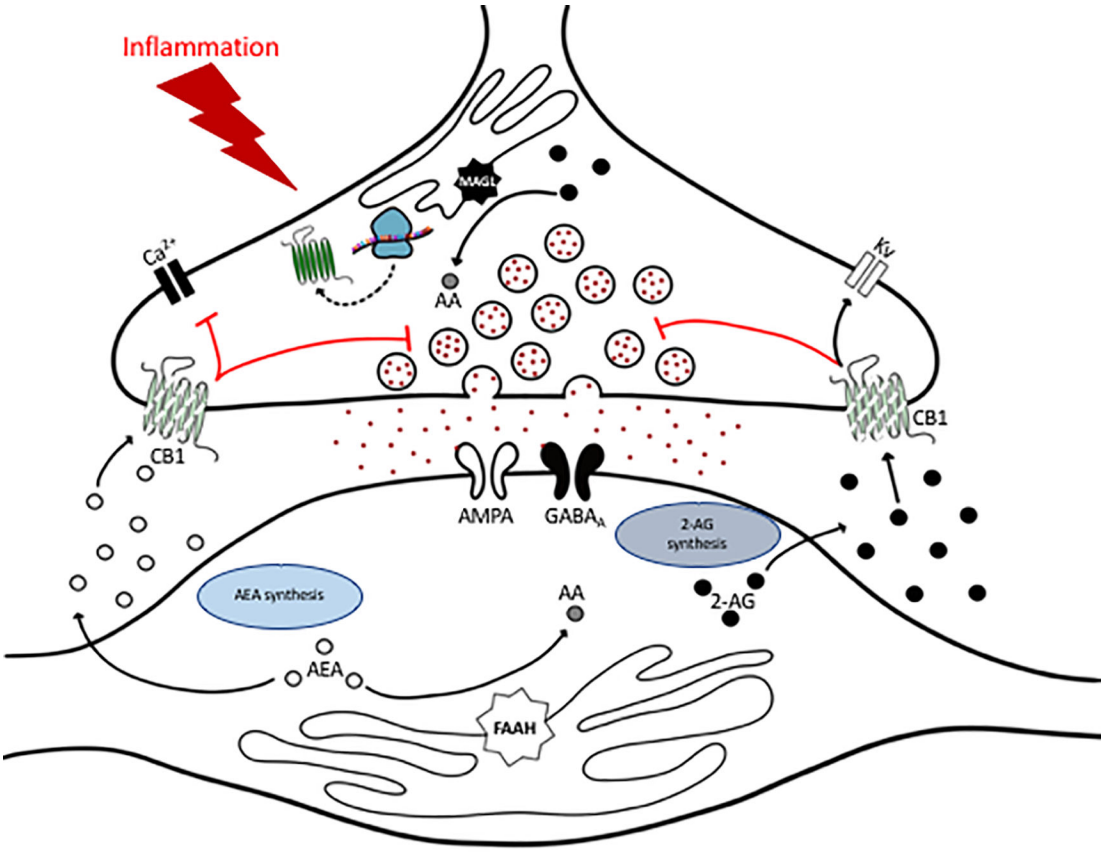

Figure 2.

Inflammation induces adaptations in presynaptic terminals. Persistent inflammation increases the release of glutamate and GABA from presynaptic terminals. This is partially due to a loss of CB1 receptor-mediated inhibition of release. At 5–7 days post-CFA, there is decreased CB1 receptor protein without a change in CB1 or CB2 receptor mRNA, AEA or 2-AG levels. However, it is not known if changes occur at earlier time points after induction of inflammation.