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REVIEW ARTICLE

Cannabinoid control of neurogenic inflammation

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A significant number of cannabinoids are known to have analgesic and anti-inflammatory properties in various diseases. Due to their presynaptic/terminal location, cannabinoid receptors can inhibit synaptic transmission and have the potential to regulate neurogenic inflammation. Neurogenic inflammation occurs when a noxious signal is detected in the periphery initiating an antidromic axon reflex in the same sensory neurone leading to depolarization of the afferent terminal. Neuropeptides are subsequently released and contribute to vasodilation, plasma extravasation and modulation of immune cells. Endocannabinoids, synthetic cannabinoids and phytocannabinoids can reduce neuroinflammation by inhibiting afferent firing and inflammatory neuropeptide release. Thus, in addition to a direct effect on vascular smooth muscle and inflammatory cells, cannabinoids can reduce inflammation by silencing small diameter neurones. This review examines the neuropharmacological processes involved in regulating antidromic depolarization of afferent nerve terminals by cannabinoids and the control of neurogenic inflammation in different diseases.

KEYWORDS
asthma, arthritis, Cannabis, inflammation, migraine, pain

1 | INTRODUCTION

Cannabis is a fast growing flowering plant originating from Central Asia, although its exact origins are obscure (Clarke & Watson, 2007; Gaoni & Mechoulam, 1964). The earliest record of cannabis use was in 2700 BC where the great Chinese deity Shennong described the hallucinatory effects of cannabis, while also noting the plant stimulated appetite and reduced painful gout (Clarke & Watson, 2007). There are three main strains of cannabis, namely, *Cannabis sativa*, *Cannabis ruderalis*, and *Cannabis indica*. *C. sativa* in particular has been used as an anaesthetic, analgesic, anxiolytic, anti-epileptic, and an appetite stimulant in many conditions (Russo, 2014). The discovery of other medical properties of cannabis has expanded to encompass anti-inflammatory, anti-cancer, and neuroprotective actions (Russo & Marcu, 2017).

Currently, there are over 545 known compounds in *C. sativa* (El Sohly & Gul, 2014). Over 100 of these molecules are cannabinoids (C_{21} terpenophenolic skeleton molecules) (El Sohly & Gul, 2014) and over 200 terpenoids (isoprene units with C_{10} or C_{15} skeletons) have been identified (Russo & Marcu, 2017). These chemicals are secreted by glandular trichromes on female plants and have been shown to have beneficial effects for the treatment of inflammation and pain (Andre, Hausman, & Guerriero, 2016; Russo & Marcu, 2017).

In addition to these plant-derived phytocannabinoids, endogenous cannabinoids have been isolated in mammals and are referred to as endocannabinoids (Lu & Mackie, 2016). The endocannabinoid system (ECS) is composed of three main constituents:- cannabinoid receptors, endogenous cannabinoids and metabolic enzymes for cannabinoid synthesis and degradation (Lu & Mackie, 2016). A list of the cannabinoids described in this review can be found in Table 1.

Cannabinoid receptors were discovered in 1990 (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990), the **CB_1 receptor** is a GPCR with seven-transmembrane spanning domains (Alexander et al., 2019;

Abbreviations: 2-AG, 2-arachidonoylglycerol; ACEA, arachidonyl-2′-chloroethylamide; CBD, cannabidiol; CPZ, capsazepine; ECS, endocannabinoid system; NAPE, N-arachidonoylphosphatidylethanolamide; NAPE-PLD, N-arachidonoylphosphatidylethanolamide PLD; NGF, nerve growth factor; PEA, palmitoylethanolamide; PTX, pertussis toxin; SP, substance P; THC, tetrahydrocannabinol; TRP, transient receptor potential; VIP, vasoactive intestinal protein.

TABLE 1 List of cannabinoids and their known targets

Cannabinoid	Target/Receptor
Endocannabinoids	
N-arachidonoyldopamine	CB_1, TRPV1
anandamide	CB_1, CB_2, TRPV1, GPR55, PPARα, PPARγ
2-Arachidonoyl glycerol (2-AG)	CB_1, CB_2, GPR55
Noladin ether	CB_1, CB_2, GPR55, PPARα
Phytocannabinoids	
Cannabidiol (CBD)	CB_2, GPR55, TRP
Δ^9-tetrahydrocannabinol (THC)	CB_1, CB_2
Synthetic cannabinoids	
Arachidonyl-2′-chloroethylamide (ACEA)	CB_1
CP55,940	CB_2
GW833972	CB_1, CB_2
GW842166	CB_2
HU210	CB_1, CB_2
JWH-015	CB_2
JWH-133	CB_2
R-(+)-methanandamide	CB_1
WIN55,212-2	CB_1, CB_2
Antagonists/inverse agonists	
AM251	CB_1
AM630	CB_2
SR141716A	CB_2

Howlett et al., 2002). The CB_1 receptor is predominantly located in the CNS (Herkenham et al., 1990) but has also been detected on the terminals of peripheral nerves (Richardson, Aanonsen, & Hargreaves, 1998), the gastrointestinal system and the reproductive system (Zou & Kumar, 2018). Localized to the terminals of nerve fibres (Howlett, 2002; Nyíri, Cserép, Szabadits, Mackie, & Freund, 2005), the CB_1 receptor has been implicated in inhibiting retrograde signalling resulting in the inhibition of neurotransmitter release and synaptic transmission (Howlett et al., 2002). CB_1 receptors have also been discovered on various immune cells and can promote both pro-inflammatory and anti-inflammatory actions (Bouaboula et al., 1993; Howlett et al., 2002). The **CB_2 receptor** was discovered in 1993 (Munro, Thomas, & Abu-Shaar, 1993) and was previously known as the peripheral cannabinoid receptor and originally thought to be only located on the cell membrane of immune cells and immune-mediating organs (Alexander et al., 2019; Howlett et al., 2002; Turcotte, Blanchet, Laviolette, & Flamand, 2016). However, CB_2 receptors have also been found in the CNS (Gong et al., 2006) and on sensory nerve terminals in the periphery (Griffin et al., 1997). Pertussis toxin (PTX) sensitivity of both cannabinoid receptors demonstrates coupling to $G_{i/o}$ proteins (Howlett, Qualy, & Khachatrian, 1986). Both CB_1 and CB_2 receptor activation can inhibit the release of pro-inflammatory mediators as a result of adenyl cyclase (AC) inhibition (Matsuda et al., 1990), calcium channel deactivation (Guo, 2004) and stimulation of the MAPK/ERK pathway (Howlett et al., 2002; Kobayashi, Arai, Waku, & Sugiura, 2001; Wartmann, Campbell, Subramanian, & Burstein, 1995; Zou & Kumar, 2018).

Atypical cannabinoid receptors are also involved in cannabinoid cell signalling (Caterina et al., 1997). **Transient receptor potential (TRP) channels** are a family of ligand-gated cation channels mainly found on primary afferent neurones/terminals (Caterina, 2014; Caterina et al., 1997). TRP channels have been implicated in nociceptive signalling through activation by noxious stimuli in the peripheral environment and subsequent depolarization of the sensory nerve terminal (Caterina et al., 1997). Endocannabinoids have been shown to bind to TRP channels where they can modulate these nociceptive responses (Akopian, Ruparel, Jeske, Patwardhan, & Hargreaves, 2008). Other atypical cannabinoid receptors include the GPCR 55 (**GPR55**) which binds several cannabinoid ligands including **HU210**, **JWH-015** and **R-(+)-methanandamide** (Mackie & Stella, 2006; Sawzdargo et al., 1999). Unlike classical cannabinoid receptors, GPR55 does not appear to couple with $G_{i/o}$ proteins (Mackie & Stella, 2006). Opioid receptors located on peripheral nerves are known to be involved in reducing neurogenic inflammation (Barin & McDougall, 2003) and cannabinoids have the ability to bind allosterically to these receptors. Cannabinoids can also target **peroxisome proliferator-activated receptors** (PPARs; NRC1) which are known to be involved in mediating inflammation and pain. For example, in a model of multiple sclerosis, the synthetic cannabinoid ligand **R-(+)-WIN55,212-2** was found to inhibit the expression of adhesion molecules in brain endothelial cells and attenuate lymphocyte extravasation from the cerebral vasculature. This effect was blocked by the **PPARγ (NCRC3)** antagonist **GW9662** (Mestre et al., 2009), thereby implicating this family of receptors in cannabinoid-mediated neuroinflammation. Taken together, it is evident that the physiological effects of cannabinoids go far beyond the endocannabinoid system, which makes targeted therapy using these compounds a challenge.

1.1 | Neurogenic inflammation

The concept of neurogenic inflammation was first postulated by Bayliss (1901) and is summarized in Figure 1. The study stated that peripherally located nerve fibres caused vasodilation in the hind limbs of dogs when stimulated by mechanical, chemical or thermal stimuli, suggesting that afferent fibres could also fire in an antidromic direction (Bayliss, 1901). These local antidromic currents were termed the "axon reflex" which is responsible for the vascular flare observed following tissue injury. This activation of sensory neurones leads to an inflammatory response called neurogenic inflammation (Bayliss, 1901). Primary afferents have been further implicated in neurogenic inflammation by application of the chemical irritant capsaicin which is known to selectively activate transient receptor potential vanilloid-1 (**TRPV1**) ion channels (Caterina, Rosen, Tominaga, Brake, & Julius, 1999; Jancsó, Jancsó-Gábor, & Szolcsányi, 1967). Local injection of capsaicin into skin can cause pain, tissue oedema and

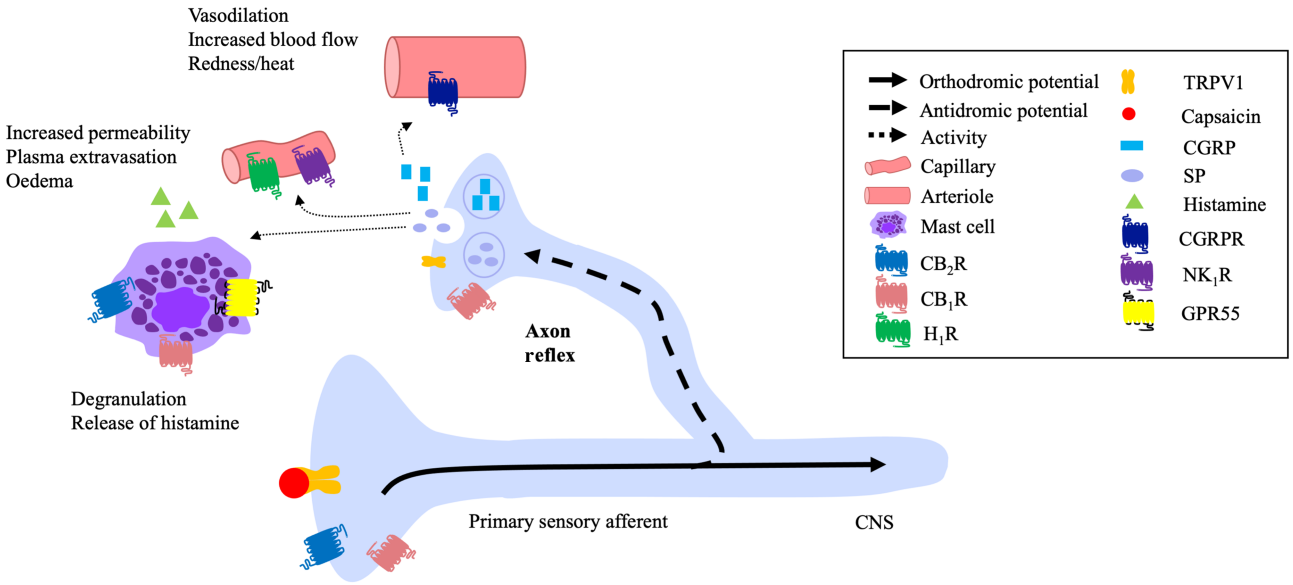

FIGURE 1 Antidromic neurogenic release of neuropeptides from primary afferent nerve terminals and resulting effects on vascular and immune targets. CB_1 receptor (R), CB_2 receptor, CGRP receptor; GPR55, GPCR 55; H_1 receptor; NK_1 receptor and TRPV1

hyperaemia which persists despite sectioning of the peripheral nerve at the site of injection (Jancsó et al., 1967).

Several pro-inflammatory neuropeptides have been shown to be released in response to antidromic nerve stimulation (Brain, 1997; Escott & Brain, 1993) and capsaicin injection (Brain, 1997; Hughes & Brain, 1994). These include **substance P** (SP), **neurokinin A** (NKA), **CGRP** and **vasoactive intestinal peptide** (VIP) (Brain, 1997). Both SP and NKA are members of the tachykinin family and act through **NK_1 receptors** on endothelial cells in post-capillary venules (Brain, 1997) leading to an increase in vascular permeability (Brain & Williams, 1989; Foreman, Jordan, Oehme, & Renner, 1983; Lembeck & Holzer, 1979). This increased permeability leads to fluid leakage resulting in oedema (Brain & Williams, 1989; Foreman et al., 1983; Lembeck & Holzer, 1979). SP can also indirectly influence plasma extravasation by activating and promoting degranulation of mast cells resulting in **histamine** release (Foreman et al., 1983). SP has been implicated in neutrophil accumulation through up-regulation of adhesion molecules (Zimmerman, Anderson, & Granger, 1992), specifically intercellular adhesion molecule-1 (Nakagawa, Sano, & Iwamoto, 1995). CGRP is a potent dilator of peripheral arterioles (Brain, Williams, Tippins, Moris, & MacIntyre, 1985) through both **NO**-dependent and -independent mechanisms (Russell, King, Smillie, Kodji, & Brain, 2014). VIP contributes to neurogenic inflammation by inducing vasodilation (Wilkins, Chung, Tublitz, Wong, & Minson, 2004) and promoting degranulation of mast cells (Theoharides et al., 2012), similar to the effects of SP (Foreman et al., 1983).

Small diameter afferents not only alter vascular tone and permeability, they also communicate with immunocytes to regulate tissue inflammation (Chiu, von Hehn, & Woolf, 2012). Mast cells, leukocytes and lymphocytes all express neuropeptide receptors on their cell surface which when activated leads to cellular degranulation or exocytosis culminating in the local release of inflammatory mediators (Coderre, Basbaum, & Levine, 1989; Dines & Powell, 1997). Furthermore, these neurotransmitters have the potential to recruit immunocytes to the site of inflammation (Smith, Barker, Morris, MacDonald, & Lee, 1993).

The inflammatory neuropeptides released from nociceptors can bind to their respective receptor on the nerve ending leading to neuronal sensitization and pain. SP, CGRP and VIP have all been shown to sensitize nociceptors in various tissues and are key mediators in the generation of pain (Carlton, Zhou, & Coggeshall, 1996; Schuelert & McDougall, 2006; Schwenger, Dux, de Col, Carr, & Messlinger, 2007). The localization of cannabinoid receptors on afferent nerve terminals means that they are ideally situated to control afferent activity and modulate pain in the periphery.

The aim of this review is to highlight the profusion of evidence that shows that endocannabinoids, synthetic cannabinoids and phytocannabinoids can alleviate neurogenic inflammation. The potential therapeutic value of cannabinoids in modulating neurogenic inflammation in various disease models will also be discussed.

2 | CANNABINOID CONTROL OF NEUROGENIC INFLAMMATION

2.1 | Endocannabinoids

The discovery of CB receptors throughout the human body prompted the search for innate compounds that serve to activate these receptors (Zou & Kumar, 2018). Endocannabinoids are endogenous lipid compounds that can interact with cannabinoid and cannabinoid-like receptors (Battista, Di Tommaso, Bari, & Maccarrone, 2012). Unlike other signalling molecules, endocannabinoids are only synthesized on demand

by local precursors within the cell and cell membrane (Di Marzo et al., 1994). A large number of endocannabinoids have been identified including n-3 and n-6 polyunsaturated fatty acid N-acylethanolamines and monoacylglycerols (Alharthi et al., 2018; Battista et al., 2012). Of all the endocannabinoids, **anandamide** (N-arachidonoylethanolamine) and **2-arachidonoylglycerol** (2-AG) are the most commonly researched (Battista et al., 2012; Howlett et al., 2002). The biosynthesis of endocannabinoids is complex and involves a vast array of enzymes and substrates (Muccioli, 2010). Fundamentally, anandamide is synthesized by the hydrolysis of N-arachidonoylphosphatidylethanolamide (NAPE) by a Ca^{2+}-sensitive NAPE-selective PLD (NAPE-PLD). While anandamide is only produced on demand, NAPE-PLD is constitutively expressed in its active form and can therefore rapidly respond to endocannabinoid demands. Anandamide is broken down by **fatty acid amide hydrolase** into arachidonic acid and ethanolamine. 2-AG is formed by the hydrolysis of DAG by the enzyme **DAG lipase**. The biosynthesis of 2-AG also occurs on demand in response to cellular depolarization leading to profound Ca^{2+} influx. The enzyme responsible for 2-AG degradation is monoacylglycerol lipase, which converts 2-AG into arachidonic acid and glycerol. The enzymes and substrates responsible for endocannabinoid synthesis are located in the cell membranes of postsynaptic neurones, while the molecular machinery responsible for endocannabinoid degradation is located presynaptically. With respect to peripheral nerve endings, endocannabinoid synthesis and degradation occurs in the distal aspect of the axons.

The presence of CB_1 and CB_2 receptors on sensory nerve terminals and their inhibitory effect on neuronal activity suggest that the endocannabinoid system has the potential to moderate neurogenic inflammation and pain (Figure 2a). Richardson, Kilo and Hargreaves (1998) showed that local application of anandamide significantly inhibited carrageenan-induced paw oedema, reduced protein extravasation and decreased locally released CGRP from rat skin. These anti-inflammatory effects were not observed when anandamide was administered contralaterally and were reversed when experimental cohorts were pretreated with the CB_1 receptor inverse agonist **rimonabant** (Richardson, Kilo, & Hargreaves, 1998).

In the pithed rat preparation, anandamide decreased vasodilation following electrical stimulation of primary afferent nerves (Marichal-Cancino, Altamirano-Espinoza, Manrique-Maldonado, Maassenvandenbrink, & Villalón, 2014) and these responses were prevented by a CB_1 antagonist, but not CB_2, GPR55 or TRPV1 antagonists (Marichal-Cancino et al., 2014). Conversely, anandamide was unable to reverse the vasodilatatory effect of exogenously administered CGRP (Marichal-Cancino et al., 2014). The inhibitory effects of anandamide on electrically induced vasodilatation but not exogenous CGRP-induced vasodilatation suggest that anandamide was acting locally on sensory nerve terminals and that the response was peripherally mediated since the spinal cord had been severed (Marichal-Cancino et al., 2014).

The endocannabinoid **noladin ether** (Sugiura, Kodaka, & Nakane, 1999) has been found to inhibit sensory neurotransmission in rat mesenteric arterial beds (Duncan, Millns, et al., 2004). At concentrations of 0.1–3 μM, direct application of noladin ether inhibited neurogenically mediated hyperaemia in mesenteric arterioles and this effect was blocked by PTX treatment (Duncan, Millns, et al., 2004). Additionally, no inhibitory effects were observed with exogenously applied CGRP nor did noladin ether have any effect on capsaicin-induced calcium responses in dorsal root ganglion cells (Duncan, Millns, et al., 2004). The authors concluded that the

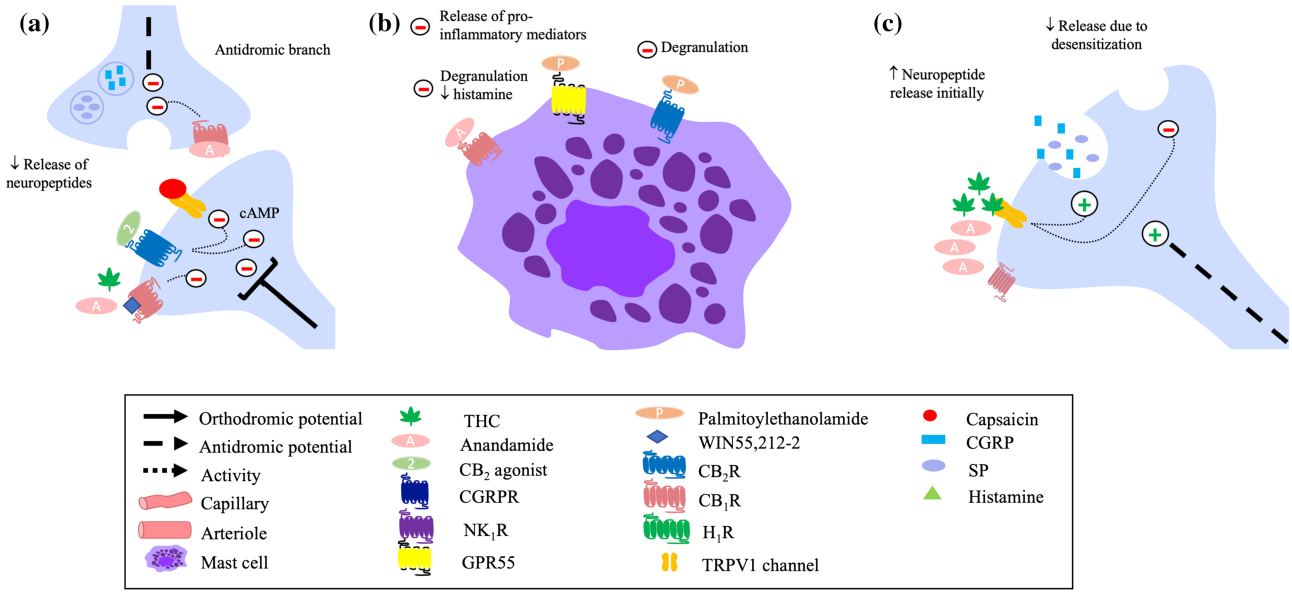

FIGURE 2 Endocannabinoids, phytocannabinoids, and synthetic cannabinoids modulate neurogenic inflammation through CB_1 receptor-mediated inhibition of nociceptive firing and neuropeptide release from primary afferents (a), through TRPV1 desensitization of afferent terminals (b), and through CB_1 receptor (R), CB_2 receptor and GPR55-mediated inhibition of mast cell degranulation (c)

atypical endocannabinoid noladin ether inhibits sensory neurotransmission by a terminal, PTX-sensitive (G_i/G_o), non-cannabinoid or TRPV1-dependent mechanism (Duncan, Millns, et al., 2004).

Other studies found that endocannabinoid-dependent neuropeptide modulation is concentration dependent. Ahluwalia, Urban, Bevan, and Nagy (2003) reported that anandamide concentrations under 1 μM inhibit both basal and capsaicin-induced CGRP release through a CB_1 receptor mechanism. In contrast, higher anandamide concentrations evoked higher levels of CGRP release equivalent to that of capsaicin-induced peptide release, which was reversed by administration of the TRPV1 antagonist **capsazepine** (CPZ) (Ahluwalia et al., 2003). These findings were replicated by Nemeth et al. (2003) who reported that inflammatory neuropeptide release could be reduced with low concentrations of anandamide (10^{-6} M) in a CB_1 receptor-dependent manner. However, at higher concentrations of anandamide the inhibitory effect of the endocannabinoid on neuropeptide release was deemed to be TRPV1 dependent. Weller, Reeh, and Sauer (2011) later supported these findings using high concentrations of the stable analogue (R)-(+)-methanandamide and confirmed the TRPV1 pathway by using TRPV1 knockout mice. These studies demonstrated that these particular endocannabinoids evoked a dual inhibition of neuropeptide release and hence neurogenic inflammation which was either CB_1 receptor dependent (low concentrations) or TRPV1 dependent (higher concentrations) (Ahluwalia et al., 2003; Nemeth et al., 2003; Weller et al., 2011).

In the isolated skin preparation, Engel et al. (2011) found that low concentrations of anandamide inhibited CGRP release while higher concentrations of the endocannabinoid increased neuropeptide levels. Heat-evoked CGRP release, however, was attenuated by high concentrations of anandamide. The reversal of these effects in a TRPV1 knockout model, but not CB_1 receptor knockouts, substantiates a desensitizing role of anandamide through TRPV1 channels, but only at higher concentrations (Figure 2b).

In addition to attenuating neuropeptide release and subsequent mitigation of neurogenic inflammation, endocannabinoids such as anandamide have also been shown to alter mast cell degranulation (Cantarella et al., 2011; Mazzari, Canella, Petrelli, Marcolongo, & Leon, 1996; Nam et al., 2016; Sugawara et al., 2012). Mazzari et al. (1996) demonstrated that oral treatment of mice with the CB_2 agonist LG2110/1 (**PEA or palmidrol**) reduced the number of mast cells that underwent SP-induced degranulation. This reduction in the secretagogue action of connective tissue mast cells by LG2110/1 culminated in a reduction in plasma extravasation and oedema. Similarly, SP-induced human mast cell degranulation could be inhibited by anandamide administration, however the CB_1 antagonist **AM251** had no effect on mast cell degranulation, suggesting that the anandamide had to be exogenously applied (Sugawara et al., 2012). Cantarella et al. (2011) proposed that anandamide attenuated the release of pro-inflammatory mediators such as nerve growth factor (NGF) from human mast cells by activating GPR55. Nam et al. (2016) also reported a reduction of the pro-inflammatory mediator histamine by anandamide from the rat basophilic leukaemia mast cell line RBL-2H3 through a CB_1 receptor mechanism. Preventing the degranulation of mast cells and the subsequent release of inflammatory neuropeptides (Figure 2c) is yet another example of how some endocannabinoids have the potential to ameliorate neurogenic inflammation.

Several endocannabinoids are also involved in regulating immune cell function. The glycoprotein CD200R is expressed on the surface of macrophages and B and T lymphocytes where its activation causes the reduction in inflammatory cytokine production (Jenmalm, Cherwinski, Bowman, Phillips, & Sedgwick, 2006). In a multiple sclerosis model, increasing endocannabinoid tone with the anandamide uptake inhibitor UCM-707 reduced the production of the inflammatory cytokine **IL-1b** while increasing levels of the anti-inflammatory cytokine **IL-10** (Hernangomez et al., 2014). Microglia, which are the resident macrophage in the CNS, also express cannabinoid receptors (Carlisle, Marciano-Cabral, Staab, Ludwick, & Cabral, 2002). Activation of microglial CB_2 receptor with anandamide inhibited ERK-1/2 phosphorylation leading to reduced pro-inflammatory **iNOS** production in multiple neuroinflammatory conditions (Rom & Persidsky, 2013).

Mediators that promote endocannabinoid synthesis and inhibitors of endocannabinoid hydrolysis are also key modulators of neurogenic inflammation. For example, the endogenous lipid **palmitoylethanolamide** (PEA) promotes anandamide and 2-AG production by inhibiting fatty acid amide hydrolase and stimulating DAGL activity, respectively (Di Marzo et al., 2001; Petrosino et al., 2019). Treatment with palmitoylethanolamide attenuated SP-induced degranulation of RBL-2H cells (Petrosino et al., 2019), demonstrating that boosting endocannabinoid tone has the potential to reduce neurogenic inflammation. Elsewhere, blockade of 2-AG hydrolysis with monoacylglycerol lipase inhibitors caused a reduction in pain reactivity in response to noxious thermal and mechanical stimuli (Mulvihill & Nomura, 2013). Monoacylglycerol lipase inhibitors also reduced prostaglandin E2 (PGE_2) production which is a known promoter of neurogenic inflammation (Jang, Kim, & Hwang, 2020; Kress, Guthmann, Averbeck, & Reeh, 1999). It should be noted that in *in vivo* experiments, the drugs that modulate endocannabinoid synthesis/breakdown are typically administered systemically, however the alteration in endocannabinoid tone occurs locally in the tissues where they can directly alter peripheral neuronal activity.

2.2 | Phytocannabinoids

The cannabis plant contains over 100 different cannabinoids whose levels vary depending upon strain and growing conditions. The majority of phytocannabinoids occur in acidic form in the plant and require decarboxylation by heating and light before becoming bioactive in humans. Physiological characterization of the phytocannabinoids is still in its infancy with the vast majority of research focusing on the psychoactive compound **Δ^9-tetrahydrocannabinol** (THC) and the non-psychotropic cannabinoid, **cannabidiol** (CBD). Less abundant phytocannabinoids include cannabigerol, **cannabinol** and cannabichromene. There is significant anecdotal and scientific evidence which shows that medical cannabis has anti-inflammatory properties in a number of chronic diseases such as arthritis, multiple sclerosis,

cancer and inflammatory bowel disease. Plant-derived CBD, for example, can act on immunocytes to reduce prostaglandin and cytokine production by interfering with COX activity and stimulating the MAPK pathway, respectively. A few of the plant-based cannabinoids also have the propensity to modulate neurogenic inflammation by acting on the endocannabinoid system (Duncan, Millns, et al., 2004; Qin et al., 2008; Wilkinson, Kendall, & Ralevic, 2007). The psychoactive cannabinoid THC significantly inhibited both vasorelaxation and CGRP release in mesenteric arterial beds following electrical field stimulation (Wilkinson et al., 2007). However, CGRP release was increased at higher concentrations of THC. The non-selective TRP channel blocker **ruthenium red**, but not cannabinoid receptor antagonists, prevented the inhibition, suggesting a TRP channel-mediated modulation of pro-inflammatory neuropeptide release (Wilkinson et al., 2007). Low concentrations of THC also inhibited capsaicin and heat-induced CGRP release in rodent skin, which was prevented by co-administration with AM251 or in CB_1 receptor knockout mice (Engel et al., 2011). The group also showed that THC concentrations exceeding 100 μM increased basal CGRP release on its own but reduced CGRP release when noxious stimuli were applied. The anti-neurogenic effects of THC were found to be TRPV1 dependent as this action was mitigated in TRPV1 knockout mice (Engel et al., 2011).

Non-psychoactive CBD and cannabinol also demonstrated a TRP-dependent mechanism in modulating pro-inflammatory neuropeptide release in peripheral tissues (Qin et al., 2008). These phytocannabinoids heightened CGRP levels significantly higher than baseline measurements, but, similar to THC-evoked responses, they could only be inhibited by the non-selective TRP blocker ruthenium red but not cannabinoid receptor antagonists (Qin et al., 2008). Calcium-dependent, ionotropic glutamate receptor-dependent (**MK-801**, **CNQX**), and G protein-dependent (G_i/G_o) signalling were ruled out due to a lack of effect with calcium channel blockers and PTX (Qin et al., 2008).

2.3 | Synthetic cannabinoids

Based on the structure–function relationship of natural cannabinoids, a growing number of synthetic ligands have been developed that selectively bind to cannabinoid receptors (Pertwee, 2010). The synthetic cannabinoids are subdivided into four main groups based on their chemical structure. Classical cannabinoid receptor agonists consist of dibenzopyran derivatives such as **HU210** and **JWH-133**. Non-classical cannabinoid agonists, such as **CP55,940**, are bicyclic or tricyclic analogues of THC. The third group is the eicosanoid cannabinoid receptor ligands which includes the endocannabinoid analogues R-(+)-methanandamide and **arachidonyl-2′-chloroethylamide** (ACEA). Finally, aminoalkylindole cannabinoids have a unique structure unlike the other synthetic cannabinoid subtypes and include JWH-015 and R-(+)-WIN55,212-2.

With respect to neurogenic inflammation, synthetic cannabinoids have been found to influence peripheral nerve activity and consequently inflammatory neuropeptide release. Electrical stimulation of isolated rat mesenteric artery beds revealed that the cannabinoid agonists HU210, WIN55,212-2, and CP55,940 inhibited CGRP-induced vasorelaxation in a concentration-dependent manner (Duncan, Kendall, & Ralevic, 2004; Ralevic & Kendall, 2001). Of note, this inhibitory effect was not evident with exogenously applied CGRP confirming a direct effect on peptidergic nerves (Duncan, Kendall, & Ralevic, 2004; Ralevic & Kendall, 2001). Antagonist studies indicate a possible CB_1 receptor-mediated inhibition of neurogenic inflammation for WIN55,212-2 and CP55,940 (Duncan, Kendall, & Ralevic, 2004) and a non-cannabinoid mechanism for HU210 (Ralevic & Kendall, 2001). Contrasting evidence by Tumati et al. (2009) shows that sustained application of WIN55,212-2 for 24 h increased basal levels of CGRP in rat neonatal dorsal root ganglia. Increased basal CGRP levels were attenuated with treatment of the CB_1 antagonist AM251 and the PKA inhibitor **H-89** (Tumati et al., 2009). This research suggests that, unlike the anti-neurogenic effects of acute treatment, sustained cannabinoid administration may contribute to pain and inflammation by stimulating inflammatory neuropeptide release (Tumati et al., 2009).

Dvorak, Watkinson, McGlone, and Rukwied (2003) also demonstrated that transdermal application of HU210 prevented histamine-induced increases in blood flow, flare responses, and itching sensations (Dvorak et al., 2003). In contrast, HU210 seemingly increased plasma extravasation when co-administered with histamine (Dvorak et al., 2003). The authors postulated that the reductions in blood flow and flare may stem from reduced excitability of the sensory afferents resulting in reduced production and release of neuropeptides, subsequently preventing vasodilation and NO production (Dvorak et al., 2003).

Selective CB_2 receptor agonists have also been used in characterizing neurogenic inflammation (Duncan, Kendall, & Ralevic, 2004). For example, JWH-015 inhibited vasorelaxation generated by electrical stimulation of small diameter sensory nerve fibres but did not inhibit vasorelaxation induced by exogenously applied CGRP (Duncan, Kendall, & Ralevic, 2004). The anti-neurogenic effects of JWH-015 were not reversed by application of CB_1/CB_2 antagonists (Duncan, Kendall, & Ralevic, 2004), suggesting a non-cannabinoid mechanism for this neurovascular inhibition. Anand et al. (2008) demonstrated a CB_2-mediated inhibition of capsaicin-induced neurogenic currents and calcium uptake in both human and guinea pig dorsal root ganglia (DRG) samples. Elsewhere, the CB_2 agonists GW833972 and GW842166 reduced whole-cell currents in response to capsaicin application, while also providing a significant inhibition of calcium influx (Anand et al., 2008). This calcium inhibition was ultimately reversed by the CB_2 antagonist **AM630** and excess cAMP but was unaffected by **SR141716A** and **naloxone** (Anand et al., 2008). The authors hypothesized that these agonists may work by depleting cAMP, thus preventing the capsaicin response through TRPV1 (Anand et al., 2008).

Synthetic cannabinoids have also been shown to alter neurogenic inflammation induced by TRP channel activation. Peripheral administration of the CB_1 agonist ACEA inhibited mustard oil-induced immunoreactive CGRP release in rat hind paw samples highlighting a link between cannabinoid receptors and transient receptor potential

ankyrin 1 (TRPA1) ion channels (Ruparel, Patwardhan, Akopian, & Hargreaves, 2011). Interestingly, these effects were not observed in TRPV1 knockout mice or in cells expressing mutated TRPV1 cation channels (Ruparel et al., 2011).

3 | EVIDENCE OF CANNABINOID CONTROL OF NEUROGENIC INFLAMMATION IN PRECLINICAL DISEASE MODELS

While the fundamental principles underlying the involvement of the endocannabinoid system in altering sensory neurotransmission and neurogenic inflammation have been described, the role of cannabinoids in various disease states is less complete. A summary of the preclinical evidence in animal models is highlighted in Tables 2–4.

3.1 | Arthritis

Various arthritis models exhibit an antidromic neurogenic component which can drive joint disease resulting in joint damage, neutrophil accumulation, vasodilatation and pain (Ahmed, Srinivasan, Theodorsson, Schultzberg, & Kreicbergs, 1995; Levine et al., 1984). In animal knee joints, low frequency stimulation of joint nerves caused synovial hyperaemia indicative of a neurogenic inflammatory response (Karimian, McDougall, & Ferrell, 1995; McDougall, Karimian, & Ferrell, 1994). These vasodilatory effects were mediated by peripheral release of NO, SP, CGRP and VIP (McDougall & Barin, 2005; McDougall & Ferrell, 1996; McDougall, Ferrell, & Bray, 1999; McDougall, Karimian, & Ferrell, 1995). Synovial levels of SP and CGRP are elevated in models of arthritis (Ahmed et al., 1995; Levine et al., 1984), while the number of SP and CGRP containing fibres have also been found to increase in rat, cat and human knees (Hanesch, Heppelmann, & Schmidt, 1997; Larsson, Ekblom, Henriksson, Lundeberg, & Theodorsson, 1991; McDougall, Bray, & Sharkey, 1997). Clearly, there is a strong neurogenic component to joint inflammation.

Cannabinoids have been shown to reduce neurogenic inflammation in joints (Table 2). The first indication that cannabinoids can act locally in the joint was demonstrated electrophysiologically where the synthetic CB_1 agonist ACEA reduced afferent firing in response to noxious mechanical stimulation (Schuelert & McDougall, 2008). The antinociceptive effect of ACEA was augmented in osteoarthritic joints, suggesting that the endocannabinoid system could be a promising target for the alleviation of arthritis pain and inflammation. Preventing the breakdown of anandamide using fatty acid amide hydrolase inhibitors is another strategy that has been used to reduce neurogenic inflammation in arthritis models (Krustev et al., 2017). Treatment of inflamed knees with the fatty acid amide hydrolase inhibitor **URB 597** reduced rolling leukocytes following electrical stimulation of the saphenous nerve (Krustev et al., 2017). The endocannabinoid-induced

TABLE 2 Endocannabinoid, synthetic cannabinoid and phytocannabinoid modulation of neurogenic inflammation in preclinical models of arthritis. ECS, endocannabinoid system.

Model	Cannabinoid/ECS mediator	Dose/application	Receptor/ proposed mechanism	Result	Reference
Electric stimulation—saphenous nerve	URB 597	0.3 $mg \cdot kg^{-1}$ Topical—over exposed joint	GPR55	↓ Rolling leukocytes Reversed by O-1918	Krustev, Muley, & McDougall, 2017
Sodium monoiodoacetate (MIA) rat model of osteoarthritis	CBD	100–300 μg Topical—over exposed joint or s.c.	TRPV1 CB_2	Improved weight bearing and mechanical allodynia ↓ Type III and IV nerve firing ↓ Rolling and adherent leukocytes No effect when given contralaterally (allodynia) Improved allodynia, rolling, and adherent reductions reversed by SB366791; rolling also blocked by AM630	Philpott, O'Brien, & McDougall, 2017
	KML29	700 μg i.artic.	CB_1 and CB_2	↓ Allodynia and leukocyte trafficking	Philpott & McDougall, 2020
Freund's complete adjuvant (FCA) rat model of inflammatory arthritis	CBD	0.6–62.3 $mg \cdot day^{-1}$ Transdermal	N/A	↓ Joint oedema (6.2—Improved pain scores) ↓ Heat hypersensitivity ↓ CGRP immune-reactivity (spinal)	Hammell et al., 2016

TABLE 3 Endocannabinoid, synthetic cannabinoid, and phytocannabinoid modulation of neurogenic inflammation in preclinical models of asthma. ECS, endocannabinoid system; PEA, palmitoylethanolamide

Model	Cannabinoid/ECS mediator	Dose/application	Receptor/proposed mechanism	Result	Reference
Electric field-, capsaicin-, NKA-induced bronchoconstriction Capsaicin-induced SP release (guinea pig)	AEA PEA	0.0288–28.8 μM i.v. 0.003–3.3 μM i.v.	CB_2 K^+ channel	↓ (anandamide/PEA) electric bronchoconstriction No effect on NKA-induced bronchoconstriction ↓ (PEA only) capsaicin-induced bronchoconstriction Reversed by SR144528 Reversed by K^+ channel blocker (NS1619) ↓ (anandamide/PEA) SP release	Yoshihara, Morimoto, Ohori, Yamada, & Abe, 2005
Capsaicin/neurokinin A-induced guinea pig bronchoconstriction Rat cigarette smoke induction (guinea pig)	WIN55,212-2	0.1 $ml \cdot kg^{-1}$ i.v.	CB_2 K^+ channel	↓ Capsaicin-induced bronchoconstriction No effect of NKA-induced constriction ↓ Plasma extravasation No effect on SP-induced extravasation Both reversed by SR144528 and K^+ channel blocker (NS1619)	Yoshihara et al., 2005
Antigen-induced plasma extravasation (ovalbumin inhalation)	WIN55,212-2 FK888	0.001–0.1 $mg \cdot kg^{-1}$ i.v. 1 $mg \cdot kg^{-1}$ i.v.	CB_2 NK_1	↓ Plasma extravasation Reversed by SR144528 FK888 + WIN showed a greater ↓ in plasma extravasation	Fukuda, Abe, & Yoshihara, 2010
Electric-/capsaicin-/NKA-activated afferent fibres (guinea pig) Capsaicin-induced SP release	WIN55,212-2 JWH-133	0.0191–19.1 μM Added directly 0.1–100 μM	CB_2 K^+ channel CB_2	↓ Electrical and capsaicin-induced contraction No effect on NKA-induced contraction ↓ Electrical-induced contraction No effect on NKA-induced contraction Reversed by SR145528 K^+ channel antagonists prevented reductions ↓ (JWH and WIN) SP release	Yoshihara, Morimoto, Yamada, Abe, & Arisaka, 2004

reduction in leukocyte trafficking was abolished with the co-administration of the GPR55 receptor antagonist O-1918 but persisted in the presence of CB_1 and CB_2 antagonists (Krustev et al., 2017). This suggests that a non-classical cannabinoid receptor was responsible for the endocannabinoid amelioration of neurogenic inflammation in this acute inflammatory model (Krustev et al., 2017).

Treatment of osteoarthritic rats with the monoacylglycerol lipase inhibitor **KML29** reduced joint pain and inflammation in a CB receptor-dependent manner (Philpott & McDougall, 2020). Since 2-AG can also be broken down by **COX-2**, the study tested a combination of **KML29** and **celecoxib** and found that the amalgamation of the two drugs was more efficacious than the individual components.

Local application of phytocannabinoids, such as CBD (Costa, Trovato, Comelli, Giagnoni, & Colleoni, 2007; Hammell et al., 2016; Philpott et al., 2017), has also been shown to reduce joint afferent firing and antidromic neuropeptide release in various arthritis models (Table 2). In a rat model of osteoarthritis, CBD dose-dependently reduced joint nociceptor firing and reduced leukocyte trafficking in

TABLE 4 Endocannabinoid, synthetic cannabinoid, and phytocannabinoid modulation of neurogenic inflammation in preclinical models of migraine. ECS, endocannabinoid system.

Model	Cannabinoid/ECS mediator	Dose/application	Receptor/proposed mechanism	Result	Reference
Dural vessel dilation (electrical, CGRP/capsaicin/NO induced)	anandamide	1–10 mg·kg^{-1} i.v.	CB_1	↓ Electric-, capsaicin- (1–3 mg·kg^{-1}), CGRP-, NO-induced (3–10 mg·kg^{-1}) vasodilation Reversed by AM251	Akerman, 2004
Dural electrical stimulation	anandamide WIN55,212-2	10 mg·kg^{-1} i.v. 1 mg·kg^{-1} i.v.	TRPV-1 and CB_1 CB_1	↓ A-fibre firing in presence of CPZ ↓ C-fibre firing Reversed by SR141716A ↓ A- and C-fibre firing Reversed by SR141716A	Akerman, Holland, & Goadsby, 2007
Basal dural functioning	anandamide	100 nM to 10 μM Added to cranial window	TRPV-1 and CB_1	↑ % blood flow (100 nM to 1 μM) ↓ % blood flow (10 μM)	Dux, Deák, Tassi, Sántha, & Jancsó, 2016
Capsaicin-/K^+-induced stimulation of the trigeminal nerve afferent	WIN55,212-2	25–50 μM Direct application	? Not CB_1/CB_2 or TRPV1	↑ CGRP (WIN55,212-2) Reversed by ruthenium red No effect on capsaicin-induced CGRP No effect on forskolin-stimulated cAMP levels ↓ K^+-induced CGRP levels	Price, Patwardhan, Akopian, Hargreaves, & Flores, 2004

the synovial vasculature (Philpott et al., 2017). This response was attenuated by the TRPV1 antagonist **SB366791** (Philpott et al., 2017). Thus, CBD is able to reduce neurogenic inflammation by desensitizing TRPV1 ion channels leading to a reduction in afferent firing rate and subsequent inflammatory neuropeptide release (Philpott et al., 2017). Hammell et al. (2016) demonstrated similar effects in an inflammatory model of arthritis. Transdermal application of CBD reduced knee joint oedema, improved heat hyperalgesia, reduced immune cell filtration and lowered spinal levels of CGRP (Hammell et al., 2016). Since no changes in CGRP levels were detectable in dorsal root ganglia, the alteration of peripheral neurogenic inflammation could not be confirmed (Hammell et al., 2016). Another study using a rat model of inflammatory arthritis showed that CBD reduced **endothelial NOS** production in a TRPV1-dependent manner (Costa et al., 2007). The proposed TRPV1 mechanism of analgesia, and reduction of a primary CGRP-induced vasoactive mediator, suggests an inhibitory effect of CBD on neurogenic inflammation in joints (Costa et al., 2007).

3.2 | Asthma

Asthma is considered a chronic inflammatory disease of the airways typically instigated by allergens and chemical irritants (Maggi, Giachetti, Dey, & Said, 1995). Neurogenic mechanisms contributing to asthmatic inflammation have been described in detail (Joos, Germonpre, & Pauwels, 2000; Maggi et al., 1995). Neuropeptide-containing nerve fibres have been identified throughout the respiratory tract (Maggi et al., 1995) and SP levels are elevated in asthmatic bronchoalveolar lavage fluid (Joos et al., 2000). Furthermore, chemical irritants such as cigarette smoke induce the release of neuropeptides through a TRPA1 mechanism, leading to bronchoconstriction and alveolar plasma extravasation (Andrè et al., 2008).

Asthmatic neurogenic inflammation has most commonly been modelled in guinea pigs (Yoshihara et al., 2004; Yoshihara, Morimoto, Ohori, Yamada, & Abe, 2005; Yoshihara, Morimoto, Ohori, Yamada, Abe, & Arisaka, 2005; Table 3). The endocannabinoid anandamide was able to reduce electrically stimulated guinea pig bronchoconstriction and capsaicin-induced SP release (Yoshihara, Morimoto, Ohori, Yamada, Abe, & Arisaka, 2005). The CB_2 antagonist **SR144528** and Ca^{2+} activated K^+ channel blockers, **iberiotoxin** and **charybdotoxin**, were used to prevent these inhibitory effects (Yoshihara, Morimoto, Ohori, Yamada, Abe, & Arisaka, 2005). The maxi-K^+ channel opener, **NS1619**, showed similar inhibitions of bronchoconstriction and plasma extravasation (Yoshihara, Morimoto, Ohori, Yamada, Abe, & Arisaka, 2005). Similarly, WIN55,212-2 and JWH-133 showed a dose-dependent inhibition of capsaicin-induced bronchoconstriction, which was reversed by a CB_2 antagonist but not by a CB_1 antagonist (Yoshihara, Morimoto, Ohori, Yamada, & Abe, 2005). The inhibition of cigarette smoke-induced plasma extravasation was also prevented solely by the CB_2 antagonist (Yoshihara, Morimoto, Ohori, Yamada, & Abe, 2005). Neither NKA-induced bronchoconstriction or SP-induced plasma extravasation was affected by the endocannabinoid system

(Yoshihara, Morimoto, Ohori, Yamada, & Abe, 2005). These data suggest that improvements in asthma may be due in part to the CB_2-mediated silencing of sensory nerve terminals, ultimately preventing the release of pro-inflammatory neuropeptides (Yoshihara, Morimoto, Ohori, Yamada, Abe, & Arisaka, 2005). Further studies showed that combined administration of WIN55,212-2 with an NK_1 receptor antagonist (FK888; L-alaninamide)) produced a marked improvement in pulmonary plasma extravasation compared to the NK_1 antagonist alone (Fukuda et al., 2010). This observation suggests that WIN55,212-2 is able to reduce SP release from C-fibre terminals and inhibit neurogenic inflammation in the lung (Fukuda et al., 2010).

3.3 | Migraine

Migraines are a prevalent neurovascular disorder characterized by unilateral head pain often accompanied by nausea and hypersensitivity to light or sound (Burstein, Noseda, & Borsook, 2015). Pathophysiological research of migraines suggests that these symptoms are a result of the activation of trigeminovascular neurons and peripheral dural afferents (Burstein et al., 2015). Initial studies found that stimulation of trigeminal afferents resulted in increased release of neuropeptides such as CGRP within the trigeminal circulation (Goadsby & Edvinsson, 1993). In humans, infusion of CGRP can cause migraine-like headaches in healthy volunteers suggesting a neurogenic component to the disorder (Lassen et al., 2002).

Localization of CB_1 receptor along the trigeminal tract and trigeminal afferents have sparked interest in determining whether the endocannabinoid system can intervene in neurogenic-induced migraine (Richardson, Aanonsen, & Hargreaves, 1998). *In vivo* testing of endocannabinoids has shown promising reductions in neurogenic inflammation in animal migraine models (Akerman, 2004; Akerman et al., 2007; Price et al., 2004; Table 4). For example, intravenous administration of anandamide (1–3 $mg{\cdot}kg^{-1}$) reduced the diameter of both capsaicin-induced and electrically stimulated dilated vessels, while only higher concentrations of anandamide (3–10 $mg{\cdot}kg^{-1}$) were able to significantly prevent CGRP- and NO-induced vasodilatation within the dura (Akerman, 2004). Anandamide-induced amelioration of vasorelaxation was inhibited by a CB_1 antagonist (Akerman, 2004). This study suggests that the endocannabinoid anandamide can have CB_1 receptor-mediated inhibitory effects on neurogenic vasodilatation of trigeminal blood vessels (Akerman, 2004). A second study demonstrated that anandamide could significantly inhibit C-fibre firing in the dura mater of the trigeminocervical complex while a combination of anandamide and the TRPV1 antagonist capsazepine was required to inhibit A-δ fibre activity (Akerman et al., 2007). This study further showed that the non-selective cannabinoid agonist WIN55,212-2 imparted a significant inhibition of A-δ and C-fibre firing that was subsequently inhibited by the CB_1 antagonist SR141716A; CB_2 receptors were not involved in this process (Akerman et al., 2007).

A more recent study showed that topical anandamide had only a minor effect on meningeal blood flow whereas another endocannabinoid N-arachidonoyldopamine caused significant hyperaemia (Dux et al., 2016). The vaso-relaxing effect of N-arachidonoyldopamine occurred via capsaicin-sensitive nerves and could be blocked by a TRPV1 ion channel antagonist as well as a CGRP antagonist. Thus, in the meninges, N-arachidonoyldopamine has the ability to cause neurogenic inflammation. In contrast, the synthetic cannabinoid WIN55,212-2 produced conflicting results when applied to trigeminal sensory afferent neurones (Price et al., 2004). The synthetic cannabinoid evoked CGRP release from trigeminal afferents when calcium was also present in the extracellular space (Price et al., 2004). The cannabinoid-induced CGRP release was only prevented by ruthenium red and not capsazepine, suggesting that these actions were mediated by a non-specific TRP channel (Price et al., 2004). In the same study, WIN55,212-2 had no effect on capsaicin-induced CGRP release or forskolin-induced cAMP accumulation but did reduce potassium-induced CGRP release from trigeminal afferents (Price et al., 2004). These reductions were not affected by either cannabinoid receptor antagonists and were not PTX sensitive, suggesting a non-classical receptor/channel mechanism (Price et al., 2004).

4 | SUMMARY

Endocannabinoids, synthetic cannabinoids and phytocannabinoids can reduce neurogenic inflammation by inhibiting neuropeptide release from primary afferent nerve endings, although some of these effects are highly dose dependent. Cannabinoids can also inhibit the crosstalk between nerves, immunocytes and mast cells leading to a reduction in cellular degranulation and the release of pro-inflammatory mediators. The anti-neurogenic effects of cannabinoids occur within a variety of cell types through interactions with both typical cannabinoid receptors and atypical receptors linked to the endocannabinoid system. Since many chronic inflammatory diseases have a neurogenic component, it will be important for future studies to consider the interaction of the endocannabinoid system and peripheral nerve terminals under pathological conditions. The widespread use of medical cannabis to manage inflammatory disorders also requires greater scrutiny with a particular focus on the interplay between individual cannabis constituents. This entourage effect of phytocannabinoids, non-cannabinoid molecules, and their multitudinous metabolites on peripheral nerve terminals as they pertain to neurogenic inflammation and pain needs further investigation. Finally, more research is needed to reveal potential synergistic effects of the endocannabinoid system to other non-cannabinoid-based therapies such as opioids to improve the safety and efficacy of treatments aimed at reducing neurogenic inflammatory disorders.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org,

the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

Ahluwalia, J., Urban, L., Bevan, S., & Nagy, I. (2003). Anandamide regulates neuropeptide release from capsaicin-sensitive primary sensory neurons by activating both the cannabinoid 1 receptor and the vanilloid receptor 1 in vitro. *European Journal of Neuroscience*, *17*(12), 2611–2618. https://doi.org/10.1046/j.1460-9568.2003.02703.x

Ahmed, M., Srinivasan, G. R., Theodorsson, E., Schultzberg, M., & Kreicbergs, A. (1995). Effects of surgical denervation on substance P and calcitonin gene-related peptide in adjuvant arthritis. *Peptides*, *16* (4), 569–579. https://doi.org/10.1016/0196-9781(95)00025-F

Akerman, S. (2004). Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. *Journal of Pharmacology and Experimental Therapeutics*, *309*(1), 56–63.

Akerman, S., Holland, P. R., & Goadsby, P. J. (2007). Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. *Journal of Pharmacology and Experimental Therapeutics*, *320*(1), 64–71.

Akopian, A., Ruparel, N., Jeske, N., Patwardhan, A., & Hargreaves, K. (2008). Role of ionotropic cannabinoid receptors in peripheral antinociception and antihyperalgesia. *Trends in Pharmacological Sciences*, *30* (2), 79–84.

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., … Pawson, A. J. (2019). The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. *British Journal of Pharmacology*, *176*(Suppl 1), S21–S141.

Alharthi, N., Christensen, P., Hourani, W., Ortori, C., Barrett, D. A., Bennett, A. J., … Alexander, S. P. H. (2018). n-3 polyunsaturated N-acylethanolamines are CB2 cannabinoid receptor-preferring endocannabinoids. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids*, *1863*, 1433–1440. https://doi.org/10.1016/j.bbalip.2018.08.003

Anand, U., Otto, W. R., Sanchez-Herrera, D., Facer, P., Yiangou, Y., Korchev, Y., … Anand, P. (2008). Cannabinoid receptor CB2 localisation and agonist-mediated inhibition of capsaicin responses in human sensory neurons. *Pain*, *138*(3), 667–680.

Andre, C. M., Hausman, J.-F., & Guerriero, G. (2016). *Cannabis sativa*: The plant of the thousand and one molecules. *Frontiers in Plant Science*, *7* (February), 1–17.

Andrè, E., Campi, B., Materazzi, S., Trevisani, M., Amadesi, S., Massi, D., … Patacchini, R. (2008). Cigarette smoke-induced neurogenic inflammation is mediated by α,β-unsaturated aldehydes and the TRPA1 receptor in rodents. *Journal of Clinical Investigation*, *118*(7), 2574–2582.

Barin, A. K., & McDougall, J. J. (2003). Endomorphin-1 causes synovial hypoaemia in rat knee joints via a capsaicin-sensitive neural pathway. *Neuroscience Letters*, *344*, 21–24.

Battista, N., Di Tommaso, M., Bari, M., & Maccarrone, M. (2012). The endocannabinoid system: An overview. *Frontiers in Behavioral Neuroscience*, *6*(March), 1–7.

Bayliss, W. M. (1901). On the origin from the spinal cord of the vasodilator fibres of the hind-limb, and on the nature of these fibres. *The Journal of Physiology*, *26*(3–4), 173–209.

Bouaboula, M., Rinaldi, M., Carayon, P., Carillon, C., Delpech, B., Shire, D., … Casellas, P. (1993). Cannabinoid-receptor expression in human leukocytes. *European Journal of Biochemistry/FEBS*, *214*(1), 173–180.

Brain, S. D., & Williams, T. J. (1989). Interactions between the tachykinins and calcitonin gene-related peptide lead to the modulation of oedema formation and blood flow in rat skin. *British Journal of Pharmacology*, *97*(1), 77–82.

Brain, S. D., Williams, T. J., Tippins, J. R., Moris, H. R., & MacIntyre, I. (1985). Calcitonin gene-related peptide is a potent vasodilator. *Nature*, *313*(6003), 54–56.

Brain, S. D. (1997). Sensory neuropeptides: Their role in inflammation and wound healing. *Immunopharmacology*, *37*(2–3), 133–152.

Burstein, R., Noseda, R., & Borsook, D. (2015). Migraine: Multiple processes, complex pathophysiology. *Journal of Neuroscience*, *35*(17), 6619–6629.

Cantarella, G., Scollo, M., Lempereur, L., Saccani-Jotti, G., Basile, F., & Bernardini, R. (2011). Endocannabinoids inhibit release of nerve growth factor by inflammation-activated mast cells. *Biochemical Pharmacology*, *82*(4), 380–388.

Carlisle, S. J., Marciano-Cabral, F., Staab, A., Ludwick, C., & Cabral, G. A. (2002). Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation. *International Immunopharmacology*, *2*, 69–82.

Carlton, S. M., Zhou, S., & Coggeshall, R. E. (1996). Localization and activation of substance P receptors in unmyelinated axons of rat glabrous skin. *Brain Research*, *734*, 103–108.

Caterina, M. J. (2014). TRP channel cannabinoid receptors in skin sensation, homeostasis, and inflammation. *ACS Chemical Neuroscience*, *5*(11), 1107–1116.

Caterina, M. J., Rosen, T. A., Tominaga, M., Brake, A. J., & Julius, D. (1999). A capsaicin-receptor homologue with a high threshold for noxious heat. *Nature*, *398*(6726), 436–441.

Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature*, *389*, 816–824.

Chiu, I. M., von Hehn, C. A., & Woolf, C. J. (2012). Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nature Neuroscience*, *15*, 1063–1067.

Clarke, R., & Watson, D. (2007). Cannabis and natural cannabis medicines. In *Marijuana and the cannabinoids* (pp. 1–16). Totowa, New Jersey: Human Press Incorporated.

Coderre, T. J., Basbaum, A. I., & Levine, J. D. (1989). Neural control of vascular permeability: Interactions between primary afferents, mast cells, and sympathetic efferents. *Journal of Neurophysiology*, *62*, 48–58. https://doi.org/10.1152/jn.1989.62.1.48

Costa, B., Trovato, A. E., Comelli, F., Giagnoni, G., & Colleoni, M. (2007). The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *European Journal of Pharmacology*, *556*(1–3), 75–83.

Di Marzo, V., Fontana, A., Cadas, H., Schinelli, S., Cimino, G., Schwartz, J. C., & Piomelli, D. (1994). Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*, *372*, 686–691.

Di Marzo, V., Melck, D., Orlando, P., Bisogno, T., Zagoory, O., Bifulco, M., … de Petrocellis, L. (2001). Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells. *The Biochemical Journal*, *358*, 249–255. https://doi.org/10.1042/bj3580249

Dines, K. C., & Powell, H. C. (1997). Mast cell interactions with the nervous system: Relationship to mechanisms of disease. *Journal of Neuropathology and Experimental Neurology*, *56*, 627–640.

Duncan, M., Kendall, D. A., & Ralevic, V. (2004). Characterization of cannabinoid modulation of sensory neurotransmission in the rat isolated mesenteric arterial bed. *The Journal of Pharmacology and Experimental Therapeutics*, *311*(1), 411–419.

Duncan, M., Millns, P., Smart, D., Wright, J. E., Kendall, D. A., & Ralevic, V. (2004). Noladin ether, a putative endocannabinoid, attenuates sensory neurotransmission in the rat isolated mesenteric arterial bed via a non-CB_1/CB_2 $G_{i/o}$ linked receptor. *British Journal of Pharmacology*, *142*(3), 509–518.

Dux, M., Deák, É., Tassi, N., Sántha, P., & Jancsó, G. (2016). Endovanilloids are potential activators of the trigeminovascular nocisensor complex. *Journal of Headache and Pain*, *17*(1), 1–9.

Dvorak, M., Watkinson, A., McGlone, F., & Rukwied, R. (2003). Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. *Inflammation Research*, *52*(6), 238–245.

El Sohly, M. A., & Gul, W. (2014). Constituents of *Cannabis sativa*. In R. G. Pertwee (Ed.), *Handbook of cannabis* (pp. 3–22). Oxford, UK: Oxford University Press.

Engel, M. A., Izydorczyk, I., Mueller-Tribbensee, S. M., Becker, C., Neurath, M. F., & Reeh, P. W. (2011). Inhibitory CB1 and activating/-desensitizing TRPV1-mediated cannabinoid actions on CGRP release in rodent skin. *Neuropeptides*, *45*(3), 229–237.

Escott, K. J., & Brain, S. D. (1993). Effect of a calcitonin gene-related peptide antagonist (CGRP8-37) on skin vasodilatation and oedema induced by stimulation of the rat saphenous nerve. *British Journal of Pharmacology*, *110*(2), 772–776.

Foreman, J. C., Jordan, C. C., Oehme, P., & Renner, H. (1983). Structure-activity relationships for some substance P-related peptides that cause wheal and flare reactions in human skin. *The Journal of Physiology*, *335*, 449–465. https://doi.org/10.1113/jphysiol.1983.sp014543

Fukuda, H., Abe, T., & Yoshihara, S. (2010). The cannabinoid receptor agonist WIN 55,212-2 inhibits antigen-induced plasma extravasation in guinea pig airways. *International Archives of Allergy and Immunology*, *152*(3), 295–300.

Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society*, *86*(8), 1646–1647.

Goadsby, P. J., & Edvinsson, L. (1993). The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Annals of Neurology*, *33*(1), 48–56.

Gong, J. P., Onaivi, E. S., Ishiguro, H., Liu, Q. R., Tagliaferro, P. A., Brusco, A., & Uhl, G. R. (2006). Cannabinoid CB2 receptors: Immunohistochemical localization in rat brain. *Brain Research*, *1071*(1), 10–23.

Griffin, G., Fernando, S. R., Ross, R. A., McKay, N. G., Ashford, M. L. J., Shire, D., … Pertwee, R. G. (1997). Evidence for the presence of CB2-1ike cannabinoid receptors on peripheral nerve terminals. *European Journal of Pharmacology*, *339*(1), 53–61.

Guo, J. (2004). Endocannabinoids modulate N-type calcium channels and G-protein-coupled inwardly rectifying potassium channels via CB1 cannabinoid receptors heterologously expressed in mammalian neurons. *Molecular Pharmacology*, *65*(3), 665–674.

Hammell, D., Zhang, L. P., Ma, F., Abshire, S. M., McIlwrath, S. L., Stinchcomb, A. L., & Westlund, K. N. (2016). Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. *European Journal of Pain*, *20*(6), 936–948.

Hanesch, U., Heppelmann, B., & Schmidt, R. F. (1997). Quantification of cat's articular afferents containing calcitonin gene-related peptide or substance P innervating normal and acutely inflamed knee joints. *Neuroscience Letters*, *233*(2–3), 105–108.

Harding, S. D., Sharman, J. L., Faccenda, E., Southan, C., Pawson, A. J., Ireland, S., … NC-IUPHAR. (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: Updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Research*, *46*, D1091–D1106. https://doi.org/10.1093/nar/gkx1121

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., De Costa, B. R., & Riceo, K. C. (1990). Cannabinoid receptor localization in brain (tetrahydrocannabinol/autoradiography/basal ganglia/-hippocampus/cerebellum). *Proc. Nati. Acad. Sci. USA*, *87*(March), 1932–1936.

Hernangomez, M., Carrillo-Salinas, F. J., Mecha, M., Correa, F., Mestre, L., Loria, F., … Guaza, C. (2014). Brain innate immunity in the regulation of neuroinflammation: Therapeutic strategies by modulating CD200-CD200R interaction involve the cannabinoid system. *Current Pharmaceutical Design*, *20*, 4707–4722. https://doi.org/10.2174/1381612820666140130202911

Howlett, A. C. (2002). The cannabinoid receptors. *Prostaglandins and Other Lipid Mediators*, *68–69*(January), 619–631.

Howlett, A. C., Barth, F., Bonner, T. I., Casellas, P., Devane, W. A., Felder, C. C., … Pertwee, R. G. (2002). International union of pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacological Reviews*, *54*(2), 161–202.

Howlett, A. C., Qualy, J. M., & Khachatrian, L. L. (1986). Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs. *Molecular Pharmacology*, *29*(3), 307–313.

Hughes, S. R., & Brain, S. D. (1994). Nitric oxide-dependent release of vasodilator quantities of calcitonin gene-related peptide from capsaicin-sensitive nerves in rabbit skin. *British Journal of Pharmacology*, *111*(2), 425–430.

Jancsó, N., Jancsó-Gábor, A., & Szolcsányi, J. (1967). Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. *British Journal of Pharmacology and Chemotherapy*, *31*(1), 138–151.

Jang, Y., Kim, M., & Hwang, S. W. (2020). Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *Journal of Neuroinflammation*, *17*, 30. https://doi.org/10.1186/s12974-020-1703-1

Jenmalm, M. C., Cherwinski, H., Bowman, E. P., Phillips, J. H., & Sedgwick, J. D. (2006). Regulation of myeloid cell function through the CD200 receptor. *Journal of Immunology*, *176*, 191–199.

Joos, G. F., Germonpre, P. R., & Pauwels, R. A. (2000). Role of tachykinins in asthma. *Allergy*, *55*, 321–337.

Karimian, S. M., McDougall, J. J., & Ferrell, W. R. (1995). Neuropeptidergic and autonomic control of the vasculature of the rat knee joint revealed by laser Doppler perfusion imaging. *Experimental Physiology*, *80*(3), 341–348.

Kobayashi, Y., Arai, S., Waku, K., & Sugiura, T. (2001). Activation by 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand, of p42/44 mitogen-activated protein kinase in HL-60 cells. *Journal of Biochemistry*, *129*(5), 665–669.

Kress, M., Guthmann, C., Averbeck, B., & Reeh, P. W. (1999). Calcitonin gene-related peptide and prostaglandin E2 but not substance P release induced by antidromic nerve stimulation from rat skin in vitro. *Neuroscience*, *89*, 303–310.

Krustev, E., Muley, M. M., & McDougall, J. J. (2017). Endocannabinoids inhibit neurogenic inflammation in murine joints by a non-canonical cannabinoid receptor mechanism. *Neuropeptides*, *64*, 131–135.

Larsson, J., Ekblom, A., Henriksson, K., Lundeberg, T., & Theodorsson, E. (1991). Concentration of substance P, neurokinin A, calcitonin gene-related peptide, neuropeptide Y and vasoactive intestinal polypeptide in synovial fluid from knee joints in patients suffering from rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, *20*(5), 326–335.

Lassen, L., Haderslev, P., Jacobsen, V., Iversen, H., Sperling, B., & Olesen, J. (2002). CGRP may play a causative role in migraine. *Cephalalgia*, *22*(1), 54–61.

Lembeck, F., & Holzer, P. (1979). Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *310*(2), 175–183.

Levine, J. D., Clark, R., Devor, M., Helms, C., Moskowitz, M. A., & Basbaum, A. I. (1984). Intraneuronal substance P contributes to the severity of experimental arthritis. *Science*, *226*(4674), 547–549. https://doi.org/10.1126/science.6208609

Lu, H.-C., & Mackie, K. (2016). An introduction to the endogenous cannabinoid system. *Biological Psychiatry*, *79*(7), 516–525.

Mackie, K., & Stella, N. (2006). Cannabinoid receptors and endocannabinoids: Evidence for new players. *The AAPS Journal*, *08*(02), E298–E306.

Maggi, C. A., Giachetti, A., Dey, R. D., & Said, S. I. (1995). Neuropeptides as regulators of airway function: Vasoactive intestinal peptide and the tachykinins. *Physiological Reviews*, *75*(2), 277–322.

Marichal-Cancino, B. A., Altamirano-Espinoza, A. H., Manrique-Maldonado, G., Maassenvandenbrink, A., & Villalón, C. M. (2014). Role of pre-junctional CB1, but not CB2, TRPV1 or GPR55 receptors in anandamide-induced inhibition of the vasodepressor sensory CGRPergic outflow in pithed rats. *Basic and Clinical Pharmacology and Toxicology*, *114*(3), 240–247.

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, *346*(9), 561–564.

Mazzari, S., Canella, R., Petrelli, L., Marcolongo, G., & Leon, A. (1996). N-(2-Hydroxyethyl) hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation. *European Journal of Pharmacology*, *300*(3), 227–236.

McDougall, J. J., & Barin, A. K. (2005). The role of joint nerves and mast cells in the alteration of vasoactive intestinal peptide (VIP) sensitivity during inflammation progression in rats. *British Journal of Pharmacology*, *145*(1), 104–113.

McDougall, J. J., Bray, R. C., & Sharkey, K. A. (1997). Morphological and immunohistochemical examination of nerves in normal and injured collateral ligaments of rat, rabbit, and human knee joints. *Anatomical Record*, *248*(1), 29–39.

McDougall, J. J., & Ferrell, W. R. (1996). Inhibition of nitric oxide production during electrical stimulation of the nerves supplying the rat knee joint. *Journal of the Autonomic Nervous System*, *57*(1–2), 73–77.

McDougall, J. J., Ferrell, W. R., & Bray, R. C. (1999). Neurogenic origin of articular hyperemia in early degenerative joint disease. *The American Journal of Physiology*, *276*(3), R745–R752.

McDougall, J. J., Karimian, S. M., & Ferrell, W. R. (1994). Alteration of substance P-mediated vasodilatation and sympathetic vasoconstriction in the rat knee joint by adjuvant-induced inflammation. *Neuroscience Letters*, *174*(2), 127–129.

McDougall, J. J., Karimian, S. M., & Ferrell, W. R. (1995). Prolonged alteration of vasoconstrictor and vasodilator responses in rat knee joints by adjuvant monoarthritis. *Experimental Physiology*, *80*, 349–357.

Mestre, L., Docagne, F., Correa, F., Loria, F., Hernangomez, M., Borrell, J., & Guaza, C. (2009). A cannabinoid agonist interferes with the progression of a chronic model of multiple sclerosis by down-regulating adhesion molecules. *Molecular and Cellular Neurosciences*, *40*, 258–266. https://doi.org/10.1016/j.mcn.2008.10.015

Muccioli, G. G. (2010). Endocannabinoid biosynthesis and inactivation, from simple to complex. *Drug Discovery Today*, *15*, 474–483.

Mulvihill, M. M., & Nomura, D. K. (2013). Therapeutic potential of monoacylglycerol lipase inhibitors. *Life Sciences*, *92*, 492–497.

Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, *365*(2), 61–65.

Nakagawa, N., Sano, H., & Iwamoto, I. (1995). Substance P induces the expression of intercellular adhesion molecule-1 on vascular endothelial cells and enhances neutrophil transendothelial migration. *Peptides*, *16*(4), 721–725.

Nam, G., Jeong, S. K., Park, B. M., Lee, S. H., Kim, H. J., Hong, S. P., … Kim, B. W. (2016). Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. *Annals of Dermatology*, *28*(1), 22–29.

Nemeth, J., Helyes, Z., Than, M., Jakab, B., Pinter, E., & Szolcsanyi, J. (2003). Concentration-dependent dual effect of anandamide on sensory neuropeptide release from isolated rat trachae. *Neuroscience Letters*, *336*, 89–92.

Nyíri, G., Cserép, C., Szabadits, E., Mackie, K., & Freund, T. F. (2005). CB1 cannabinoid receptors are enriched in the perisynaptic annulus and on preterminal segments of hippocampal GABAergic axons. *Neuroscience*, *136*(3), 811–822.

Pertwee, R. G. (2010). Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Current Medicinal Chemistry*, *17*, 1360–1381.

Petrosino, S., Schiano Moriello, A., Verde, R., Allara, M., Imperatore, R., Ligresti, A., … Di Marzo, V. (2019). Palmitoylethanolamide counteracts substance P-induced mast cell activation in vitro by stimulating diacylglycerol lipase activity. *Journal of Neuroinflammation*, *16*, 274. https://doi.org/10.1186/s12974-019-1671-5

Philpott, H. T., & McDougall, J. J. (2020). Combatting joint pain and inflammation by dual inhibition of monoacylglycerol lipase and cyclooxygenase-2 in a rat model of osteoarthritis. *Arthritis Research & Therapy*, *22*, 9. https://doi.org/10.1186/s13075-020-2096-3

Philpott, H. T., O'Brien, M., & McDougall, J. J. (2017). Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. *Pain*, *158*(12), 2442–2451.

Price, T. J., Patwardhan, A., Akopian, A. N., Hargreaves, K. M., & Flores, C. M. (2004). Cannabinoid receptor-independent actions of the aminoalkylindole WIN 55,212-2 on trigeminal sensory neurons. *British Journal of Pharmacology*, *142*(2), 257–266.

Qin, N., Neeper, M. P., Liu, Y., Hutchinson, T. L., Lubin, M. L., & Flores, C. M. (2008). TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *Journal of Neuroscience*, *28*(24), 6231–6238.

Ralevic, V., & Kendall, D. A. (2001). Cannabinoid inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed. *European Journal of Pharmacology*, *418*(1–2), 117–125.

Richardson, J. D., Aanonsen, L., & Hargreaves, K. M. (1998). Anti-hyperalgesic effects of spinal cannabinoids. *European Journal of Pharmacology*, *345*(2), 145–153.

Richardson, J. D., Kilo, S., & Hargreaves, K. M. (1998). Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain*, *75*(1), 111–119.

Rom, S., & Persidsky, Y. (2013). Cannabinoid receptor 2: Potential role in immunomodulation and neuroinflammation. *Journal of Neuroimmune Pharmacology*, *8*, 608–620.

Ruparel, N. B., Patwardhan, A. M., Akopian, A. N., & Hargreaves, K. M. (2011). Desensitization of transient receptor potential ankyrin 1 (TRPA1) by the TRP vanilloid 1-selective cannabinoid arachidonoyl-2 chloroethanolamine. *Molecular Pharmacology*, *80*(1), 117–123.

Russell, F. A., King, R., Smillie, S. J., Kodji, X., & Brain, S. D. (2014). Calcitonin gene-related peptide: Physiology and pathophysiology. *Physiological Reviews*, *94*(4), 1099–1142.

Russo, E. (2014). The pharmacological history of cannabis. In R. Pertwee (Ed.), *Handbook of cannabis* (pp. 3–23). Oxford, UK: Oxford University Press.

Russo, E. B., & Marcu, J. (2017). Cannabis pharmacology: The usual suspects and a few promising leads. In *Advances in pharmacology* (1st ed., Vol. 80). Elsevier Inc.

Sawzdargo, M., Nguyen, T., Lee, D. K., Lynch, K. R., Cheng, R., Heng, H. H. Q., … O'Dowd, B. F. (1999). Identification and cloning of three novel human G protein-coupled receptor genes GPR52, ΨGPR53 and GPR55: GPR55 is extensively expressed in human brain. *Molecular Brain Research*, *64*(2), 193–198.

Schuelert, N., & McDougall, J. J. (2006). Electrophysiological evidence that the vasoactive intestinal peptide receptor antagonist VIP(6–28) reduces nociception in an animal model of osteoarthritis. *Osteoarthritis and Cartilage*, *14*, 1155–1162.

Schuelert, N., & McDougall, J. J. (2008). Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis and Rheumatism*, *58*, 145–153.

Schwenger, N., Dux, M., de Col, R., Carr, R., & Messlinger, K. (2007). Interaction of calcitonin gene-related peptide, nitric oxide and histamine

release in neurogenic blood flow and afferent activation in the rat cranial dura mater. *Cephalalgia*, *27*, 481–491.

Smith, C. H., Barker, J. N., Morris, R. W., MacDonald, D. M., & Lee, T. H. (1993). Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit granulocytic infiltration in human skin. *Journal of Immunology*, *151*, 3274–3282.

Sugawara, K., Bíró, T., Tsuruta, D., Tóth, B. I., Kromminga, A., Zákány, N., … Paus, R. (2012). Endocannabinoids limit excessive mast cell maturation and activation in human skin. *Journal of Allergy and Clinical Immunology*, *129*(3), 726–738.e8. https://doi.org/10.1016/j.jaci.2011.11.009

Sugiura, T., Kodaka, T., & Nakane, S. (1999). Evidence that the cannabinoid CB1 receptor is a 2-arachidonoylglycerol receptor. *Journal of Biological Chemistry*, *274*(5), 2794–2801.

Theoharides, T. C., Alysandratos, K.-D., Angelidou, A., Delivanis, D.-A., Sismanopoulos, N., Zhang, B., … Kalogeromitros, D. (2012). Mast cells and inflammation. *Biochimica et Biophysica Acta*, *1822*(1), 21–33.

Tumati, S., Yamamura, H. I., St John, P. A., Vanderah, T. W., Roeske, W. R., & Varga, E. V. (2009). Sustained cannabinoid agonist treatment augments CGRP release in a PKA-dependent manner. *Neuroreport*, *20*(8), 815–819.

Turcotte, C., Blanchet, M. R., Laviolette, M., & Flamand, N. (2016). The CB2 receptor and its role as a regulator of inflammation. *Cellular and Molecular Life Sciences*, *73*(23), 4449–4470.

Wartmann, M., Campbell, D., Subramanian, A., & Burstein, S. H. (1995). The MAP kinase signal transduction pathway is activated by the endogenous cannabinoid anandamide. *FEBS Letters*, *359*, 133–136.

Weller, K., Reeh, P. W., & Sauer, S. K. (2011). TRPV1, TRPA1, and CB1 in the isolated vagus nerve—Axonal chemosensitivity and control of neuropeptide release. *Neuropeptides*, *45*(6), 391–400.

Wilkins, B. W., Chung, L. H., Tublitz, N. J., Wong, B. J., & Minson, C. T. (2004). Mechanisms of vasoactive intestinal peptide-mediated vasodilation in human skin. *Journal of Applied Physiology*, *97*(4), 1291–1298.

Wilkinson, J. D., Kendall, D. A., & Ralevic, V. (2007). Δ^9-Tetrahydrocannabinol inhibits electrically-evoked CGRP release and capsaicin-sensitive sensory neurogenic vasodilatation in the rat mesenteric arterial bed. *British Journal of Pharmacology*, *152*(5), 709–716.

Yoshihara, S., Morimoto, H., Ohori, M., Yamada, Y., & Abe, T. (2005). The cannabinoid receptor agonist WIN 55212-2 inhibits neurogenic inflammations in airway tissues. *Journal of Pharmacological Sciences*, *82*, 77–82.

Yoshihara, S., Morimoto, H., Ohori, M., Yamada, Y., Abe, T., & Arisaka, O. (2005). Endogenous cannabinoid receptor agonists inhibit neurogenic inflammations in guinea pig airways. *International Archives of Allergy and Immunology*, *138*(1), 80–87.

Yoshihara, S., Morimoto, H., Yamada, Y., Abe, T., & Arisaka, O. (2004). Cannabinoid receptor agonists inhibit sensory nerve activation in guinea pig airways. *American Journal of Respiratory and Critical Care Medicine*, *170*(9), 941–946.

Zimmerman, B. J., Anderson, D. C., & Granger, D. N. (1992). Neuropeptides promote neutrophil adherence to endothelial cell monolayers. *The American Journal of Physiology*, *263*(5 Pt 1), G678–G682.

Zou, S., & Kumar, U. (2018). Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. *International Journal of Molecular Sciences*, *19*(3), 1–23.

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