Chapter 7. Endocannabinoids and migraine

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Endocannabinoids and migraine

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Endocannabinoid System and Migraine

Cannabis has been used for recreational and medicinal purposes throughout the world for many centuries. While best known for its psychotropic effects, cannabis has long been known to have analgesic, immunomodulatory, and anti-inflammatory effects. The use of cannabis as a symptomatic and prophylactic treatment of migraine was highly regarded in the 19th century. Patient self-report surveys on marijuana have been positive for a variety of symptoms including headache (Schnelle et al., 1999). El-Mallakh described three long-term daily marijuana users who developed headache after cessation of marijuana, matching clinical experience of headache being a symptom of withdrawal (El-Mallakh, 1987). Robbins and colleagues described a man with cluster headache who was able to abort an attack in 5 minutes with marijuana inhalation (Robbins et al., 1999).

Cannabinoids may offer significant “side benefits” beyond analgesia. These include anti-emetic effects, well established with Δ⁹-tetrahydrocannabinol (THC) (Pertwee, 2012). In 1915, Sir William Osler, the acknowledged father of modern medicine, proposed the treatment of migraine with Cannabis indica (Osler and McCrae, 1915), and the following year Dr. Dixon, Professor of Pharmacology at King’s College and the University of Cambridge, reported the therapeutic effects of smoked cannabis for headache treatment (Ratnam, 1916). The botanical origin of cannabis has been debated to be as far east as China, but most experts suspect it to be in Central Asia, possibly in the Pamir (Camp, 1936). Use of marijuana has long been known to cause an increase in relaxation and euphoria along with, at times, memory impairment. Marijuana can be associated paradoxically with anxiety and dysphoria in some people and this relates to a biphasic effect of cannabinoids. The reduction in anxiety is likely beneficial in the headache patient. The adverse effect on working memory is presumably due to a very high density of CB₁ receptors in the hippocampus. Marijuana is known to contain over 60 cannabinoids, which made early isolation of THC, thought to be the only mood altering constituent,
MIGRAINE PATHOGENESIS

Migraine is a neurological syndrome characterized by altered bodily perceptions, with increased sensory sensitivity to light, sound, and head movement, severe headaches, and nausea. Although the pathophysiology of migraine is to a great extent still elusive, the activation of the trigeminovascular system followed by neurogenic inflammation in the dura mater is widely recognized as one of the main mechanisms underlying migraine attacks (Moskowitz, 1993). Evidence also suggests that the *primum movens* of migraine attacks is represented by the interaction of internal or external triggers with dysfunctional brainstem centers involved in regulating pain sensation (Goadsby, 2002; Knight, 2005). Dysfunction of brainstem centers is associated with activation of the trigeminovascular system and with dilatation of cerebral blood vessels (Myers, 1999). The dilated blood vessels activate the trigeminal sensory nerve fibers mechanically, therefore inducing the release of glutamate, substance P, calcitonin gene-related peptide (CGRP), and other inflammatory neuropeptides from the sensory nerve terminals (Moskowitz et al., 1989; Moskowitz, 1993). These inflammatory chemicals irritate and further dilate blood vessels, thus inducing more release from the sensory neurons and an increase of pain impulses that are transmitted to the nucleus trigeminalis caudalis (NTC). NTC in turn relays pain signals to higher brain centers including the thalamus and cortex.

Nitric oxide (NO) has been proposed to play a crucial role in the activation of the trigeminovascular system by activating perivascular sensory afferent nerve fibers (via 5-hydroxytryptamine (serotonin) 2B/2C (5-HT₂B/2C) receptors), in the meninges, thereby contributing to the release of vasoactive neuropeptides (Messlinger et al., 2000; Strecker et al., 2002). NO may also cause additional NO formation, vasodilatation, and neurogenic inflammation, which may all further contribute to the development of migraine pain.

Various components of the immune system have been examined in relation to headache (Bruno et al., 2007). While great strides have been made in advancing our understanding of neuroimmunology, the complexities of the system make its specific role in headache pathology unclear. CGRP triggers the secretion of...
Cytokines via stimulation of CGRP receptors found on T-cells (Bruno et al., 2007). Cytokines are involved in inflammation, in modulation of the pain threshold, and also in trigeminal nerve fiber sensitization. In small trials, cytokines have been proven to precipitate headache (Rozen and Swidan, 2007). In addition, recent studies have shown that glial cells, previously thought to serve only a supportive role, are now known to directly influence the microenvironment of trigeminal ganglion neurons through gap junctions and paracrine signaling (Bruno et al., 2007). Following trigeminal activation, CGRP secreted from neuronal cell bodies activates adjacent glial cells to release NO and inflammatory cytokines, which, in turn, initiate inflammatory events in the trigeminal ganglia that lead to peripheral sensitization. The neuronal–glial signaling is thought to be an important process, ultimately leading to the initiation of migraine. The glial modulation of neurons through immune mediators is an unexplored area for new migraine medications.

**CORTICAL SPREADING DEPRESSION**

In 10% of migraineurs, painful attacks are preceded or associated with aura symptoms. The aura consists of fully reversible symptoms that precede or accompany the headache. The aura is commonly described as changes in the visual field. Visual images change, and there can be loss of focus, spots of darkness, and zigzag flashing lights. It often begins with a hazy spot close to the center of vision and can form into a star shape that further develops into a shape known as fortification (semicircular with angles). This scintillating vision consists of luminous, bright, flickering colors of the spectrum, like a prism catching light. It can be combined with a scotoma (an area of vision that appears to be obstructed or missing). The visual image fades as the headache begins. The headache is intense, throbbing, and usually contralateral to the visual field changes. Cortical spreading depression (CSD) refers to a phenomenon that manifests as a self-propagating wave of neuronal hyperexcitability followed by a transient depression (Leao, 1944). CSD is accompanied by characteristic ionic, metabolic, and hemodynamic changes and may play an essential role in some neurological disorders including migraine with aura (Somjen, 2001; Sanchez-Del-Rio et al., 2006). The hypothesis that the aura is the human equivalent of CSD has been well established (Goadsby, 2007). Propagation of a CSD-like wave in human neocortical tissues generates aura symptoms in migrainous patients (Hadjikhani et al., 2001). Furthermore, it was proposed that CSD might also trigger the rest of the migraine attacks including pain (Moskowitz, 1993).

**ENDOCANNABINOIDS AND MIGRAINE**

**CLINICAL DATA**

Based on experimental evidence of the antinociceptive action of endocannabinoids and their role in the modulation of trigeminovascular system activation, it
was hypothesized that the endocannabinoid system may be dysfunctional in migraine patients, thus suggesting the potential use of cannabinoids in the treatment of migraine and in cluster attacks refractory to the usual drugs prescribed (Sarchielli et al., 2007; Cupini et al., 2008; Russo, 2008). Additionally, it should be noted that the human gene encoding the CB₁ receptor—cnr₁—has been mapped to chromosome 6q14–15 (91.8–96.1 cM), which is situated within the region that has showed linkage with migraine (71–101 cM on chr6) (Nyholt et al., 2005). A recent study aimed to evaluate the relationship between alterations of cnr₁ gene and headache in migraineurs has reported a significant haplotypic association between cnr₁ gene and headaches as regards three highly predictive symptoms for migraine: nausea, photophobia, and disability. The results show that the risk haplotype results in attenuated CB₁ receptor expression or function, therefore making the carriers more vulnerable to migraine and also causing an alteration in the peripheral trigeminovascular activation (Juhasz et al., 2009).

Previous studies have shown that female patients suffering from episodic migraine have increased interictal CB₁ receptor binding especially in brain regions that exert top-down influences to modulate pain, supporting the idea that endocannabinoid deficiency may play a role in the pathophysiology of migraine (Van der Schueren et al., 2012). Reduced levels of anandamide (AEA) and increased levels of N-palmitoylethanolamine (PEA), an endocannabinoid-like compound that does not bind to cannabinoid receptors, were found in the cerebrospinal fluid of patients with chronic migraine (Sarchielli et al., 2007). It was suggested that the reduced levels of AEA may be associated with increased activation of the trigeminovascular system, which, in turn, may lead to increased CGRP and NO production (Akerman et al., 2004a), thus contributing to facilitate/maintain central sensitization in chronic head pain.

Perrotta et al. (2012) have demonstrated, in migraineurs evolved into chronic medication-overuse headache (MOH), an acute reduction of the activity of the enzyme fatty acid amide hydrolase (FAAH). This reduction of activity was associated with reduction of the facilitation in pain processing immediately (10 days) after withdrawal treatment. The authors have suggested that decrease of FAAH activity could be the consequence of a mechanism devoted to acutely reduce the degradation of endocannabinoids. In a previous study, Cupini et al. (2008) reported a reduction in a specific AEA membrane transporter (EMT) and FAAH levels in platelets of subjects with chronic migraine and MOH, as compared to either controls or episodic migraine group. FAAH and EMT activities observed in both chronic migraine and MOH patients did not seem to be related to differences in gender, having been observed in both sexes. Female migraineurs show increased FAAH and EMT activities, a finding that is consistent with a lowered endocannabinoid tone and perhaps a reduced concentration of AEA in blood (Cupini et al., 2006). Finally, 2-arachidonoylglycerol (2-AG) and AEA levels were significantly lower in MOH patients and chronic migraine patients than in the control subjects, without significant differences between the two patient groups. Serotonin levels were also strongly reduced in the two
patient groups and were correlated with 2-AG levels, with higher values for MOH patients (Rossi et al., 2008).

**EXPERIMENTAL DATA**

Experimental evidence shows that the antinociceptive action of endocannabinoids (eCBs), related to the modulation of trigeminovascular system activation (Akerman et al., 2007) and consequently to the inhibition of trigeminal nerve activation, may be helpful in evaluating new targets for the treatment of migraine. eCBs exert a critical control over cerebrovascular tone, by interacting with serotonergic transmission, NO production, and CGRP release (Pertwee, 2001). CB₁ receptors have been detected in the periaqueductal gray (PAG) matter, rostral ventromedial medulla, and NTC, which are potential migraine generators and pain modulators (Mailleux and Vanderhaeghen, 1992; Moldrich and Wenger, 2000).

**Studies with neurovascular models of migraine**

**Model of Nitroglycerin**

Systemic administration of nitroglycerin (NTG), an NO donor, has been used extensively as an animal model of migraine pain since NTG consistently provokes spontaneous-like migraine attacks in migraine sufferers and induces hyperalgesia in the rat through the activation of spinal and brain structures involved in nociception (Buzzi et al., 2003; Tassorelli et al., 2006). CB₁ receptors have been identified also in many of the NTG-activated areas located in the brainstem, hypothalamus, and midbrain (Mailleux and Vanderhaeghen, 1992; Moldrich and Wenger, 2000; Van Sickle et al., 2005). In a previous study, we reported significant changes in the activity of enzymes that catabolize AEA and 2-AG, and FAAH and a cytosolic monoacylglycerol lipase (MAGL), respectively, in the brainstem and hypothalamus of rats following NTG administration. In particular, in the mesencephalon NTG increased the activities of both AEA and 2-AG, thus suggesting a reduction in the endogenous levels of both enzymes. On the other hand, only FAAH was found to increase in the hypothalamus and in the medullary area that contains the NTC. In the same areas, an up-regulation of CB₁ receptor binding sites was also observed. These findings seem to suggest that AEA, rather than 2-AG, is the endocannabinoid more likely implicated in the modulation of pain originating in the cephalic area. It is noteworthy that these changes were paralleled by a reduction in NTG-induced hyperalgesia and NTG-induced c-Fos expression in the NTC (Greco et al., 2010) (Figure 7.1). In addition, URB937, an FAAH inhibitor specific for peripheral tissues, causes analgesia in animal models of pain (Clapper et al., 2010). We evaluated whether URB937 administration may alter nociceptive responses in this animal model of migraine (Greco et al., 2012). Rats received systemic NTG and URB937 before being evaluated via the tail flick test or via the formalin test. The findings showed that URB937 did inhibit NTG-induced hyperalgesia at the formalin test with only a minimal influence on the hyperalgesia at the tail flick,
suggesting that availability of AEA, probably at the meningeal level, is effective in reducing migraine pain (Greco et al., 2012).

CB$_1$ receptors are localized on fibers in the spinal trigeminal tract and spinal NTC (Tsou et al., 1998), and therefore their activation in trigeminal neurons following pretreatment with AEA might inhibit CGRP release from central terminals of primary afferent fibers, thus reducing NTG-induced c-Fos expression. Alternatively, AEA may inhibit c-Fos expression via activation of CB$_2$ receptors. Selective activation of CB$_2$ receptors indeed suppresses spinal c-Fos protein expression and pain behavior in a rat model of inflammation, following carrageenan injection in the paw (Nackley et al., 2003). In addition, when considering that NTG promotes the activity of nuclear

**FIGURE 7.1**
c-Fos expression in the nucleus trigeminalis caudalis and its modulation by anandamide.
(A): number of c-Fos-positive neurons in the group of animals treated with nitroglycerin (NTG4 h), with vehicle (CT), or with anandamide and nitroglycerin (AEA + NTG).
* $p<0.05$ vs. NTG4 h. (B) micrographs of representative sections of the nucleus trigeminalis caudalis of rats treated with nitroglycerin (left) or pretreated with AEA (right) before receiving nitroglycerin.

Data from Greco et al. (2009).
factor-kappa B (\(NF-\kappa B\))—a gene implicated in neuroinflammation—and inflammation in dura mater and NTC of rats with a time course consistent with migraine attacks in susceptible individuals (Reuter et al., 2002; Greco et al., 2005), it is conceivable that AEA might inhibit expression of proteins through a potential inhibition of \(NF-\kappa B\) inactivation (Sancho et al., 2003). In addition, in a recent study (unpublished data) we have found that AM1241, a CB\(_2\) receptor agonist, significantly reduces the nociceptive behavior of the rats made hyperalgesic by NTG administration in the second phase of the formalin test, therefore suggesting a role for CB\(_2\) receptors in this animal model of migraine. Accordingly, activation of CB\(_2\) receptors reduces spinal Fos protein expression and pain behavior in a rat model of inflammation (Nackley et al., 2003). This finding is in agreement with the analgesic effect of CB\(_2\) receptor stimulation observed in the model of carrageenan-induced inflammation (Quartilho et al., 2003; Nackley et al., 2003, 2004).

Studies with Electrical Dural Stimulation and Cutaneous Facial Receptive Field Activation of the Ophthalmic Division of the Trigeminal Nerve

Previously, responses to both electrical dural stimulation and cutaneous facial receptive field activation of the ophthalmic division of the trigeminal nerve and the effect of cannabinoid agonists and antagonists were studied (Akerman et al., 2007). The data show that AEA inhibits neurons of the trigeminovascular system only after transient inhibition of transient receptor potential vanilloid-1 (TRPV1) receptors, therefore suggesting a minor role for TRPV1 receptor in the modulation of the trigeminovascular system (Akerman et al., 2004a). The inhibition of trigeminal firing in the trigeminocervical complex is indeed reversed by the administration of a specific CB\(_1\) receptor antagonist, which demonstrates conclusively that the central effects of eCBs are CB\(_1\) receptor mediated (Akerman et al., 2007). Therefore, manipulation of CB\(_1\) receptors may involve the responses of trigeminal neurons with A- and C-fiber inputs from the dura mater. This may be a direct effect on neurons in the NTC itself, or in discrete areas of the brain that innervate these neurons.

Recently, it was reported that activation of CB\(_1\) receptors in the ventrolateral periaqueductal gray (vIPAG) attenuated dural-evoked A-fiber neurons (maximally by 19%) and basal spontaneous activity (maximally by 33%) in the rat trigeminocervical complex, but had no effect on cutaneous facial receptive field responses (Akerman et al., 2013). This inhibitory vIPAG-mediated modulation was inhibited by specific CB\(_1\) receptor antagonism, given locally, and with a 5-HT\(_{1B/1D}\) receptor antagonist, given either locally in the vIPAG or systemically. These findings demonstrate that brainstem endocannabinoids provide descending modulation of both basal trigeminovascular neuronal tone and A-fiber dural-nociceptive responses, which differs from the way the brainstem
modulates spinal nociceptive transmission. Furthermore, these data demonstrate a novel interaction between serotonergic and endocannabinoid systems in the processing of somatosensory nociceptive information, suggesting that some of the therapeutic action of triptans may be via endocannabinoid-containing neurons in the vPAG (Akerman et al., 2013). The brainstem is heavily populated with CB₁ receptors and descending modulation of trigeminovascular nociceptive transmission through midbrain nuclei (PAG and rostroventral medulla) is likely to be responsible for the quick antinociceptive effect on headache, as often voiced by marijuana users (Akerman et al., 2011).

**Studies with vascular models of migraine**

The CB₁ receptor seems to be involved in the NO/CGRP relationship that is likely to underline headache attacks. In fact, AEA is able to inhibit neurogenic dural vasodilatation, as well as CGRP-induced and NO-induced dural vessel dilation in the intravital microscopy model, although some of the blood pressure changes caused by AEA are mediated by an as-yet-unknown non-cannabinoid receptor, as suggested by the observation that AM251, a CB₁ receptor antagonist, is unable to reverse these effects (Akerman et al., 2004b).

It has been shown that AEA activating the TRPV1 receptor on trigeminal ganglion neurons may promote the release of CGRP (Tognetto et al., 2001). AEA is able to cause a dose-dependent (1, 3, and 5 mg kg⁻¹) increase in dural vessel diameter, while capsaicin (3 mg kg⁻¹), a TRPV1 receptor antagonist, and CGRP(8-37) (300 μg kg⁻¹), a CGRP receptor antagonist, attenuate AEA-induced dural vessel dilation. In addition, in rats pretreated with AM251 (3 mg kg⁻¹), the dilation induced by AEA (5 mg kg⁻¹) is unaltered, while it results attenuated by a specific TRPV1 receptor antagonist (Akerman et al., 2004a), thus confirming that AEA exerts its vasodilator effect through a mechanism dependent on TRPV1 activation, but which does not involve CB₁ receptors. This apparent discrepancy might depend on the high AEA concentrations used, as it is known that AEA activates CB₁ or TRPV1 receptors in a concentration-dependent manner (Pertwee and Ross, 2002; Van Sickle et al., 2005).

**Effect of Cannabinoid Receptor Activation on Cortical Spreading Depression**

The effects of THC as well as synthetic cannabinoid CB₁ and CB₂ receptor agonists on CSD in rat neocortical slices were investigated by Kazemi et al. (2012). THC (1–20 μM) dose-dependently suppressed cortical spreading depression (CSD) amplitude, duration, and propagation velocity. The CB₁ receptor agonist WIN 55,212-2 mesylate (1–10 μM) also significantly suppressed the field excitatory postsynaptic potentials (fEPSPs) and long-term potentiation of CSD. However, the cannabinoid CB₂ receptor agonist JWH133 (1–20 μM) did not affect CSD.
**POTENTIAL SITES AND MECHANISMS OF ACTION OF ECs**

The trigeminovascular system has long been implicated as integral to the pain, inflammation, and secondary vascular effects of migraine. This system receives inputs from other higher brain centers, such as hypothalamus, thalamus, and PAG (Bartsch et al., 2004). Therefore, activation of CB₁ receptors in these sites may influence trigeminovascular neuronal firing. CB₁ receptors are present in small neurons that express the high affinity catalytic receptor for the neurotrophin TrkA (Friedel et al., 1997), and in neurons that express substance P or CGRP in the dorsal root ganglia (Hohmann and Herkenham, 1999b; Pertwee, 2001), from where they are transported to central and peripheral terminals (Hohmann and Herkenham, 1999a). Thus, bidirectional transport of CB₁ receptors raises the question as to whether the modulation of pain by cannabinoids is centrally or peripherally mediated. The mechanisms by which cannabinoids produce their anti-migraine effects are not fully known; however, several studies have proposed different hypotheses. Figure 7.2 summarizes the potential mechanisms related to the effects of eCBs on migraine.

**EFFECTS ON THE SEROTONIN SYSTEM**

In 1985, Volfe et al. reported that THC inhibits the release of serotonin from the blood of migraine sufferers during an attack (but not at other times). However, a more profound understanding of cannabis and its action in the brain has only recently been reached with the discovery of AEA in the human brain (Devane

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**FIGURE 7.2**

Schematic drawing of the possible sites and mechanisms of action of the endocannabinoid system in the pathophysiology of migraine at the cerebral, neurovascular, and vascular levels.

*From Greco et al. (2010).*
et al., 1992). Other researches shed light on possible mechanisms of therapeutic action of the cannabinoids on migraine, suggesting the inhibitory effect of AEA and other cannabinoid agonists on rat serotonin type 3 (5-HT$_3$) receptors (Fan, 1995). AEA has been shown to potentiate 5-HT$_{1A}$ receptors, while oleamide, another endogenous brain lipid structurally related to AEA, has been shown to enhance 5-HT$_2$ receptor function in vivo (Kimura et al., 1998). Both these effects envisage a potential therapeutic effect, though never tested, for eCBs in the acute/chronic treatment of migraine.

**EFFECTS ON THE NMDA/GLUTAMATE SYSTEM**

A trigeminovascular system has long been implicated as integral to the pain, inflammation, and secondary vascular effects of migraine, linked through the NMDA/glutamate system (Storer and Goadsby, 1999). Cannabinoid agonists inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release (Shen et al., 1996). NMDA receptor antagonism was felt to be effective in eliminating hyperalgesia associated with migraine (Nicolodi and Sicuiteri, 1995), as well as a “secondary hyperalgesia” with exaggerated responses to noxious stimuli in areas adjacent to the pain. THC and phytocannabinoids also act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA, and kainate receptors (Hampson et al., 1998).

**EFFECTS ON INFLAMMATORY MOLECULES**

Although the pathophysiology of migraine is to a great extent still elusive, the activation of the trigeminovascular system followed by neurogenic inflammation in the dura mater is widely recognized as one of the main mechanisms underlying migraine attacks (Moskowitz, 1993). The anti-inflammatory contributions of THC are also extensive, including inhibition of prostaglandin E$_2$ (PGE-2) synthesis (Burstein et al., 1973), decreased platelet aggregation (Schaefer et al., 1979), and stimulation of lipoxygenase (Fimiani et al., 1999). THC has 20 times the anti-inflammatory potency of aspirin and twice that of hydrocortisone but in contrast to all non-steroidal anti-inflammatory drugs (NSAIDs), demonstrates no cyclo-oxygenase (COX) inhibition at physiological concentrations (Russo and Guy, 2006). Endocannabinoids are also rapidly generated in response to pro-inflammatory stimulation of immune cells, and they might operate a negative feedback control over the pro-inflammatory response, possibly by negatively regulating the activation of transcription factors involved in the inflammatory response (Berdyshev et al., 2001). Previous studies have shown that, in murine macrophages and splenocytes, cannabinoids and the endocannabinoid 2-AG may either activate or inhibit NF-κB activity via CB$_1$ receptor and protein kinase A-dependent mechanisms (Daaka et al., 1997).
LIMITATIONS

While the antinociceptive actions of cannabinoids are well established, their potential therapeutic use continues to be limited by their side effects profile. Clearly, the development and use of novel cannabinoid compounds for the relief of pain in humans will hinge on the ability to dissociate psychotropic effects from therapeutic ones. In addition, changing of synaptic plasticity by activation of CB₁ receptors may affect signal processing as well as learning and memory in different regions of the brain (Kazemi et al., 2012). These side effects should be taken into consideration in further development of new cannabinoid derivatives.

NEW POTENTIAL THERAPEUTIC APPROACHES

INHIBITORS OF CATABOLISM

Enhancing endocannabinoid tone has been proposed as an alternative means of activating CB₁ receptors without concomitant overt psychotropic effects associated with potent synthetic CB₁ receptor agonists. Enhancing endocannabinoid tone via FAAH or MAGL inhibition elicits anti-inflammatory effects in several animal models (Holt et al., 2005; Jayamanne et al., 2006; Booker et al., 2012). In vitro studies suggest that endocannabinoids elicit anti-inflammatory effects comparable to those of exogenous cannabinoids. Increasing AEA tone, either directly or via inhibition of its degradation or uptake, has been demonstrated to reduce the levels of pro-inflammatory cytokines and inflammatory mediators such as TNF-α, IL-1β, and NO, and to enhance the release of the anti-inflammatory cytokine IL-10 in vitro (Puffenbarger et al., 2000; Correa et al., 2009, 2010). Selective and potent inhibitors of FAAH have been developed and tested in vivo in several animal models of disease so far. Three FAAH blockers in particular seem promising for future clinical development: URB597 (Mor et al., 2004), arachidonoylserotonin (N-arachidonoyl-serotonin, AA-5-HT) (Bisogno et al., 1998), and SA73 (Sanofi-Aventis) (Zhang et al., 2007). In particular, URB597 is an irreversible FAAH inhibitor, still at the preclinical stage, with anxiety, depression, and pain as the most likely therapeutic targets (Piomelli et al., 2006). It has potent analgesic activity in models of neuropathic pain when administered orally, and it has proved efficacious following systemic administration in models of inflammatory pain (Jayamanne et al., 2006) and inflammation (Holt et al., 2005).

CB₂ RECEPTOR AGONISTS

Recently, CB₂ receptor agonists have been proposed as a valid alternative to CB₁ receptor agonists in pain modulation, either because of their mainly peripheral distribution, so they do not cause adverse central effects, or because of their capability
to inhibit signs of acute nociceptive, inflammatory, and neuropathic pain in preclinical studies (Malan et al., 2003; Li and Zhang, 2012; Murineddu et al., 2013).

Although there is a large body of evidence supporting the potential utility of selective cannabinoid CB$_2$ receptor agonists for the treatment of pain (Guindon and Hohmann, 2008), the mechanism and site of action responsible for CB$_2$-mediated analgesia remain unexplained.

**CONCLUSIONS**

In several studies, the antinociceptive effect of cannabinoids has been unequivocally demonstrated in models of inflammatory and neuropathic pain, although some controversies exist on the localization of these pain-protective effects. Migraine has numerous relationships with eCBs and a deficiency in the endocannabinoid system has been hypothesized to underlie the pathophysiology of migraine. However, biochemical studies providing a scientific basis for the potential efficacy of (endo)cannabinoids in migraine are, so far, limited.

**REFERENCES**


CHAPTER 7 Endocannabinoids and migraine


