The endocannabinoid system and migraine

Article *in* Experimental Neurology · March 2010

DOI: 10.1016/j.expneurol.2010.03.029 · Source: PubMed

Experimental Neurology 224 (2010) 85–91

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

The endocannabinoid system and migraine

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ARTICLE INFO

Article history:
Received 25 March 2010
Accepted 25 March 2010
Available online 29 March 2010

Keywords:
Anandamide
Migraine
Nitroglycerin
Pain
Platelet
Vanilloid receptors

ABSTRACT

The recently discovered endocannabinoid system (ECS), which includes endocannabinoids and the proteins that metabolize and bind them, has been implicated in multiple regulatory functions both in health and disease. Several studies have suggested that ECS is centrally and peripherally involved in the processing of pain signals. This finding is corroborated by the evidence that endocannabinoids inhibit, through a cannabinoid type-1 receptor (CB1R)-dependent retrograde mechanism, the release of neurotransmitters controlling nociceptive inputs and that the levels of these lipids are high in those regions (such as sensory terminals, skin, dorsal root ganglia) known to be involved in transmission and modulation of pain signals. In this review we shall describe experimental and clinical data that, intriguingly, demonstrate the link between endocannabinoids and migraine, a neurovascular disorder characterized by recurrent episodic headaches and caused by abnormal processing of sensory information due to peripheral and/or central sensitization. Although the exact ECS-dependent mechanisms underlying migraine are not fully understood, the available results strongly suggest that activation of ECS could represent a promising therapeutical tool for reducing both the physiological and inflammatory components of pain that are likely involved in migraine attacks.

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Introduction

The endocannabinoid system (ECS) is a recently characterized physiological system comprised of bioactive lipid compounds named endocannabinoids (ECs), their metabolic enzymes, and their receptors, the cannabinoid receptor type-1 and type-2, (CB1R and CB2R, respectively), originally identified as molecular targets of the *Cannabis sativa* active principle Δ^9-tetrahydrocannabinol (Δ^9-THC). *N*-Arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), the best characterized ECs, are amides and esters of arachidonic acid (AA).

The best characterized enzymes involved in AEA and 2-AG metabolism are the *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD) and the *sn*-1-specific diacilglycerol lipase (DAGL), respectively which synthesize them from phospholipids membrane (Okamoto et al., 2004; Bisogno et al., 2003) and fatty acid amide hydrolase (FAAH) which releases AA and ethanolamine and AA and glycerol, respectively. Nevertheless, 2-AG degradation is mainly due

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doi:10.1016/j.expneurol.2010.03.029

to a cytosolic monoacylglycerol lipase (MAGL) (Fezza et al., 2008; McKinney and Cravatt, 2005; Blankman et al., 2007). Otherwise, before hydrolysis the ECs have to be removed from the extracellular space through a purported endocannabinoids membrane transporter (EMT) (Yates and Barker, 2009).

To date, it has been well established that, many parallel biosynthetic and degradative pathways are involved in ECs metabolism (Okamoto et al., 2009; Sugiura, 2009; Wei et al., 2006; Tsuboi et al., 2007; Blankman et al., 2007).

Collectively, these findings indicate that the above-mentioned enzymes, by regulating the endogenous levels of ECs in central nervous system (CNS), are involved in the modulation of specific brain functions. Indeed, through activation of CB1R, highly expressed in several CNS areas (Tsou et al., 1998; Kano et al., 2009), ECs are able to control movement, memory, wake/sleep cycles, thermogenesis, appetite, and also nociception (Bellocchio et al., 2008; Kano et al., 2009; Sagar et al, 2009). It has been clearly demonstrated that ECs regulate these brain functions acting as retrograde neurotransmitters, since they are synthesized and released from postsynaptic neurons and bind to CB1R in the presynaptic terminal (Katona and Freund, 2008). In particular CB1R, by inhibiting the release of neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, dopamine, noradrenaline and acetylcholine, are involved in transmission and modulation of pain signals (Katona and Freund, 2008). This finding is also supported by the evidence that AEA and 2-AG are highly present in those regions involved in nociception, like the sensory terminals, the skin, dorsal root ganglia (DRG), spinal cord, periaqueductal gray (PAG) matter, and rostral ventromedial medulla (Palkovits et al., 2008).

Already Kosersky et al. (1973) showed that systemic administration of Δ^9-THC increased the threshold for paw pressure-induced vocalization following the induction of inflammation in the hind paw. Preclinical behavioural studies demonstrated that systemic administration of (endo)cannabinoids induced analgesia in animal models of both acute and persistent nociception caused by different types of noxious stimulation (i.e. thermal, mechanical, and chemical) (Walker and Hohmann, 2005). Further studies aimed to characterize the anti-nociceptive effects of (endo)cannabinoids showed that activation of the CB1R by synthetic agonists, and/or pharmacological elevation of ECs levels via inhibition of FAAH activity, reduces hyperalgesia and allodynia in animal models of neuropathic pain (La Rana et al., 2006). Additionally, the anti-nociceptive response to (endo)cannabinoids is absent or attenuated in mice lacking *cnr1* gene (encoding for CB1R) in the peripheral nociceptors (Agarwal et al., 2007), thus suggesting the involvement of peripheral CB1R in the analgesic effects exerted by (endo)cannabinoids. Whilst a proportion of the peripheral analgesic effect of ECs can be attributed to a neuronal mechanism based on the activation of CB1 receptors expressed in primary afferent neurons, the anti-inflammatory actions of ECs, mediated through CB2 receptors, also appears to contribute to local analgesic effects. CB2 receptors were originally described as being restricted to immune cells, nevertheless there is now evidence for their expression in keratinocytes (Ibrahim et al., 2005) and in human primary sensory neurons (Wotherspoon et al., 2005; Anand et al., 2008); moreover, an increased CB2R expression has been reported in human peripheral nerves after injury (Wotherspoon et al., 2005), and in central neurons upon induction of remote cell death (Viscomi et al., 2009). The involvement of CB2R in the analgesic effects of ECs is also supported by the usage of CB2R agonists, which seems to attenuate nociception in animal models of inflammatory and nociceptive pain (Anand et al., 2009). A possible CB2R-mediated mechanism could include the attenuation of NGF-induced mast cell degranulation and of neutrophil accumulation, processes that are known to contribute to the generation of inflammatory hyperalgesia (Rice et al., 2002; Beltramo, 2009). The advantage of the analgesic effect of CB2R selective agonists is mainly based on the lack of the typical psychotropic side effects of CB1R activation (Beltramo, 2009).

It should be also recalled that opioids and cannabinoids bind distinct receptors that co-localize in areas of the brain involved in the processing of pain signals, and that Δ^9-THC triggers the release of endogenous opioids and of ECs such as AEA (Welch, 2009). The synergy between opioids and cannabinoids is also supported by the findings that the latter produce opioid-sparing effects, as well as prolong the duration of analgesia and reduce opioid tolerance and dependence (Welch, 2009).

Finally, there is also evidence that a combination of small-dose cannabinoid (devoid of undesirable side effects) with non-steroidal anti-inflammatory drugs (NSAIDs), could result in analgesia without the adverse effect associated with large-dose of both cannabinoids and NSAID alone (Ulugöl et al., 2006).

On the other hand, other experiments carried out with cannabinoid receptor antagonists or *cnr1* knockout animals reported opposite results (Valverde et al., 2005). Indeed, a recent study reported that spinal ECs and CB1R, localized in inhibitory dorsal horn inter-neurons, play an unexpected role in dorsal horn pain-controlling circuits, since they mediate heterosynaptic pain sensitization (Pernía-Andrade et al., 2009).

The endocannabinoid system (ECS) and migraine

The use of *Cannabis* in the symptomatic and prophylactic treatment of migraine dates back to the XIX century (see Russo (2004) for review). 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 the Kings' 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 Plains (Camp, 1936). However, a more profound understanding of *Cannabis* and its action in the brain has only recently occurred with the discovery in the human brain of AEA, from the Sanskrit word “ananda” (or “bliss”) (Devane et al., 1992). Additional researches shed light on the possible mechanisms of therapeutic action of (endo)cannabinoids on migraine, suggesting an inhibitory effect of AEA and other cannabinoid agonists on rat serotonin type 3 (5-HT3) receptors (Fan, 1995).

Experimental animal models exploring the effects of nociceptive activation of the trigeminovascular system and aimed to understand the pathophysiology of migraine (De Vries et al., 1999) confirmed numerous relationships between the ECS and migraine.

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 has one of the main mechanisms underlying migraine attacks (Moskowitz, 1993). Evidences also suggest 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 (Knight, 2005; Goadsby, 2002). Dysfunction of brainstem centers is associated with activation of the trigeminovascular system and with dilation of cerebral blood vessels (Myers, 1999; Welch, 2003). The dilated blood vessels activate the trigeminal sensory nerve fibres mechanically, therefore inducing the release of glutamate, substance P, calcitonin gene-related peptide (CGRP), and other inflammatory neuropeptides from the sensory nerve terminals (Moskowitz, 1993; Moskowitz et al., 1989). 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 fibres (via 5-hydroxytryptamine (serotonin) 2B/2C (5-HT2B/2C) receptors), in the meninges, thereby contributing to the release of vasoactive neuropeptides (Lassen et al., 1998; Olesen et al., 1995; 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.

Endocannabinoids and migraine: clinical data

Endocannabinoid deficiency has been hypothesized to underlie the pathophysiology of migraine and recent and previous clinical studies support this idea (Russo, 2004) although biochemical studies providing a scientific basis for the potential efficacy of (endo) cannabinoids in migraine are really limited.

AEA has been shown to potentiate 5-HT1A receptors, while oleamide, another endogenous brain lipid structurally related to AEA, has been shown to enhance 5-HT2 receptor function *in vivo* (Kimura et al., 1998; Cheer et al., 1999). Both these effects let envisage a potential therapeutic effect, though never tested, for ECs in the acute/chronic treatment of migraine. In a recent report, a patient with cluster headache attacks refractory to conventional medications did respond to the treatment with marijuana and dronabinol, a synthetic Δ^9-THC (Robbins et al., 2009). This study suggests the potential use of cannabinoids in the treatment of cluster attacks refractory to usual drugs. Sarchielli et al. (2007) have reported reduced levels of AEA and increased levels of *N*-palmitoylethanolamine (PEA), an endocannabinoid-like compound that does not bind to cannabinoid receptors, in the cerebrospinal fluid of patients with chronic migraine. It is possible that reduced levels of AEA may be associated with an increased activation of the trigeminovascular system in migraine patients, which in turn may lead to increased CGRP and NO production, as suggested by the experimental data obtained by Akerman et al. (2004a) using intravital microscopy. Theoretically, the reduction of AEA levels, and hence the reduced inhibitory effect of ECS, may contribute to facilitate/maintain central sensitization in chronic head pain, therefore providing an additional mechanism which contributes to CGRP release and NO production, together with nerve growth factor and brain-derived neurotrophic factor (BDNF) (Sarchielli et al., 2001, 2002). The increased levels of PEA seem less relevant in this context and may just result from a compensatory response to reduced levels of AEA (Sarchielli et al., 2007).

To date, it is not clear whether the observed changes in the ECS are a specific response to migraine or they can be extended to other chronic head pain conditions. Rossi et al. (2008) reported that chronic psychoemotional stress impairs CBR-mediated control of GABA transmission in the striatum of mice. 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). This evidence might well explain the strong prevalence of migraine in women. However, to make the picture more complex, the same authors more recently (Cupini et al., 2008) have reported a reduction in EMT and FAAH levels in platelets of subjects with chronic migraine and medication overuse headache, as compared to either controls or episodic migraine group. FAAH and EMT activities observed in both chronic migraine and medication overuse headache patients did not seem to be related to differences in gender, having been observed in both sexes. Taken together, these findings suggest a possible gender-specific modulation of migraine in its episodic form, while more complex mechanisms are likely involved when the disease becomes chronic. Nevertheless, it should be noted that the human gene encoding for CB1R–*cnr1*–has been mapped to chromosome 6q14–15 (91.8–96.1 cM), which is situated within the region that 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).

Endocannabinoids and migraine: experimental data

Recent experimental evidences have shown that the anti-nociceptive action of ECs, related to the modulation of trigeminovascular system activation (Akerman et al., 2007), and consequently to inhibition of trigeminal nerve activation, may be helpful in evaluating new targets for the treatment of migraine. Endocannabinoids exert a critical control on cerebrovascular tone, by interacting with serotonergic transmission, NO production, and CGRP release (Pertwee, 2001). CB1Rs have been detected in PAG matter, rostral ventromedial medulla and NTC, which are potential migraine generators and pain, modulators (Moldrich and Wenger, 2000; Mailleux and Vanderhaeghen, 1992). Systemic administration of nitroglycerin (NTG), a 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 it induces a condition of hyperalgesia in the rat through the activation of spinal and brain structures involved in nociception (Buzzi et al., 2003; Tassorelli et al., 2006). CB receptors have been identified also in many of the NTG-activated areas located in the brainstem, hypothalamus and midbrain (Van Sickle et al., 2005; Moldrich and Wenger, 2000; Mailleux and Vanderhaeghen, 1992). In a recent study, we have reported significant changes in the activity of enzymes that catabolize AEA and 2-AG, FAAH and MAGL respectively, in the brainstem and hypothalamus of rats following NTG administration (Fig. 1). In particular, in the mesencephalon NTG increased the

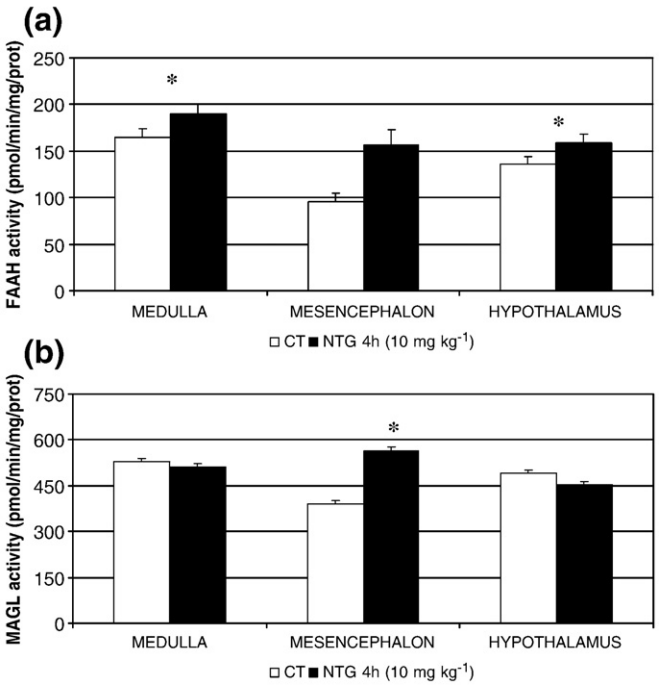

Fig. 1. Activity of FAAH (panel a) and of MAGL (panel b) in selected cerebral areas of rats following nitroglycerin (NTG 4 h) or vehicle (CT) administration. Substrate was 10 μM [^{3}H]AEA or 10 μM [^{3}H]2-oleoylglycerol, for FAAH or MAGL respectively. Data are expressed as mean ± SD; *p<0.05 vs. CT. (Data from Greco et al., 2009)

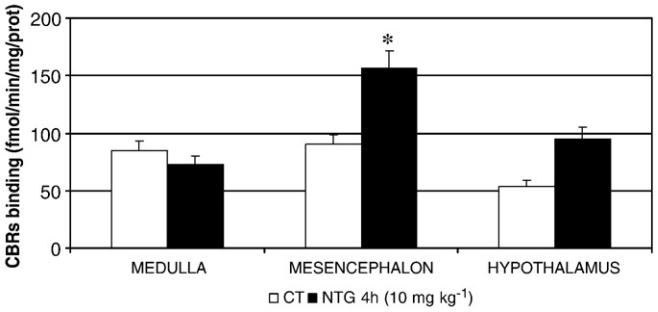

Fig. 2. Binding of 0.4 nM [^{3}H]CP55.940 to CBRs in selected cerebral areas of rat following nitroglycerin (NTG 4 h) or vehicle (CT) administration. Data are expressed as mean ± SD; *$p<0.05$ vs. CT. (Data from Greco et al., 2009)

activities of both enzymes, thus suggesting a reduction in the endogenous levels of both AEA and 2-AG. On the other hand, only FAAH was found to increase in the hypothalamus and in the medulla area that contains NTC (Fig. 1). In the same areas, an up-regulation of CBR binding sites was also observed (Fig. 2). 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., 2009) (Fig. 3).

An important role for AEA in migraine pain is also suggested by the observation that AEA (20 mg kg^{-1}) reduces NTG-induced c-Fos expression observed in the NTC (Fig. 3) (Greco et al., 2009). AEA possesses a vasodilator activity and it has been identified also in endothelial cells, confirming its potential role in the modulation of the vascular system (Battista et al., 2004; Maccarrone et al., 2000). The trigeminovascular system receives inputs from other higher brain centers, such as hypothalamus, thalamus, and PAG (Bartsch et al., 2004; Shields and Goadsby, 2005). Therefore, activation of CB receptors in these sites may influence trigeminovascular neuronal firing. However, CB1Rs are expressed also on axon terminals of primary sensory neurons, such as in the nociceptive areas of spinal cord, DRG and trigeminal ganglia, and their expression is partially co-localized in CGRP- and substance P-expressing neurons (Pertwee, 2001; Price et al., 2003). Therefore, it is also possible that (endo)cannabinoids exert their antinociceptive effect through peripheral CB1 receptors (Agarwal et al., 2007). In line with this, using knockout mice it has been demonstrated that CB1 receptors in the GABAergic or cortical glutamatergic neurons are not essential for the analgesic effect of Δ^9-THC (Monory et al., 2007), but deletion of *cnr1* in the peripheral nociceptors considerably reduced the analgesic effect of local and systemic cannabinoids. CB1 receptors are localized on fibers in the spinal trigeminal tract and spinal NTC (Tsou et al., 1998), therefore their activation in trigeminal neurons following pre-treatment 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 CB2R. Selective activation of CB2R 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 factor-kappa B (NF-κB)–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-κB inactivation (Sancho et al., 2003).

CB1R 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 CB1R antagonist, is unable to reverse these effects (Akerman et al., 2004a).

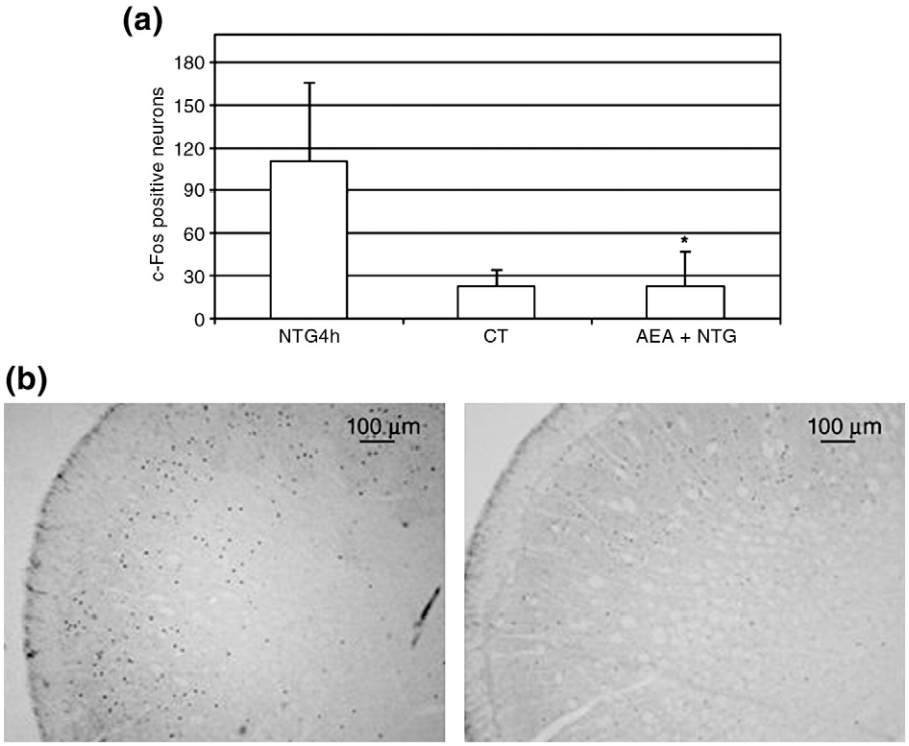

Fig. 3. c-Fos expression in the nucleus trigeminalis caudalis, and its modulation by anandamide. Panel a: number of c- Fos positive neurons in the group of animal treated with nitroglycerin (NTG 4 h), with vehicle (CT), or with anandamide and nitroglycerin (AEA + NTG). *$p<0.05$ vs. NTG 4 h. Panel b: micrographs of representative sections of the nucleus trigeminalis caudalis of rats treated with nitroglycerin (left) or pre-treated with AEA (right) before receiving nitroglycerin (data from Greco et al., 2009).

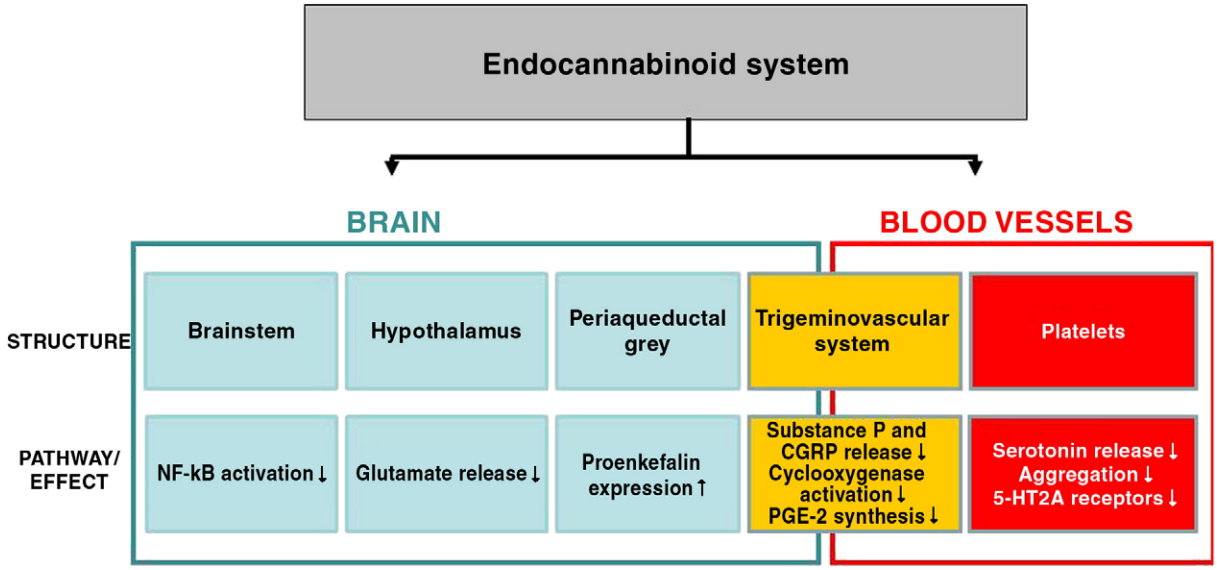

Fig. 4. Schematic drawing of the possible sites and mechanisms of action of the endocannabinoid system in the pathophysiology of migraine at the cerebral, neurovascular and vascular levels.

It should be recalled that AEA is now widely referred as a true "endovanilloid" since it activates the transient receptor potential vanilloid receptor (TRPV1), a ion channel receptor primarily located on sensory nerves and activated by specific stimuli capable of initiating and amplifying pain and inflammation (Szallasi and Blumberg 1999; Tóth et al., 2009). It has been shown that AEA also activates the TRPV1 receptor on trigeminal ganglion neurons, thus promoting the release of CGRP (Tognetto et al., 2001). This EC is able to cause a dose-dependent (1, 3 and 5 mg kg^{-1}) increase in dural vessel diameter, while capsazepine, a TRPV1 receptor antagonist (3 mg kg^{-1}), and a CGRP receptor antagonist (300 μg kg^{-1}) attenuate AEA-induced dural vessel dilation. In addition, in rats pre-treated 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., 2004b), thus confirming that AEA exerts its vasodilator effect through a mechanism depending on TRPV1 activation, but that does not involve CB1R. This apparent discrepancy might depend on the high AEA concentrations used, as it is known that AEA activates CB1R or TRPV1 receptors in a concentration-dependent manner (Di Marzo and Deutsch, 1998; Pertwee and Ross, 2002; Sarker and Maruyama, 2003; Van Sickle et al., 2005).

Recently, responses to both dural electrical 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 TRPV1 receptor, therefore suggesting a minor role for TRPV1 receptor in the modulation of the trigeminovascular system (Akerman et al., 2004b). The inhibition of trigeminal firing in the trigeminocervical complex is indeed reversed by the administration of a specific CB1R antagonist, which demonstrates conclusively that the central effects of ECs are CB1R-mediated (Akerman et al., 2007). Therefore, manipulation of CB1 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. In Fig. 4 the potential mechanisms related to the effects of ECs on migraine are summarized.

Conclusions

In several studies, the anti-nociceptive 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. Additionally, some studies have reported hyperalgesia in response to systemically administered antagonists of CB receptors, whereas several others have reported evidence against a role for the endocannabinoid system in the tonic inhibition of pain (Walker and Hohmann, 2005). Global, classical *cnr1* knockout mice from two different genetic backgrounds have yielded conflicting results in this regard (Zimmer et al., 1999; Ledent et al., 1999). Numerous studies have demonstrated that activation of CB receptors individually at several of these diverse loci can reduce nociceptive transmission, but the relative contributions of each of these sites to the total analgesic effects of systemic (endo)cannabinoids remains ambiguous (Walker and Hohmann, 2005). Recently, it was reported that also the peripheral ECS may have an important role in the endogenous pain control mechanisms (Agarwal et al., 2007). This study did not elucidate the relative contributions of CB1Rs and CB2Rs, but it suggested that both cannabinoid receptors, as others yet-unidentified CB receptors (Mackie and Stella, 2006) and potential synergistic effects between them, may contribute to cannabinoid analgesia. In conclusion, activation of ECS represents an interesting potential tool for reducing physiological as well as inflammatory pain–the types of pain most likely involved in migraine attacks–although the involved mechanisms need further investigation.

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