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Review

Functional neuroanatomy of the endocannabinoid system

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Abstract

Several components of the endocannabinoid system have been fully characterized. Among them are two types of cannabinoid receptors (termed CB_1 and CB_2), endogenous ligands for those receptors (referred to as "endocannabinoids"), and specific enzymes responsible for their degradation and inactivation. The study of the distribution and abundance of these elements in the central nervous system has provided the basis for the well-known effects of exogenous (both natural and synthetic) and endogenous cannabinoids. In addition, recent developments also support the idea that the endocannabinoid system plays a critical neuromodulatory role in the central nervous system. For instance, cannabinoid CB_1 receptor activation is known to modify the release of several neurotransmitters, such as glutamate and gamma-aminobutyric acid. However, we still lack knowledge on fundamental aspects of the physiological roles of this system. Interestingly, changes in the distribution and activity of some of these components of the endocannabinoid system have been reported under different pathological conditions, suggesting their possible involvement in the pathogenesis of these diseases. As comprehensive excellent reviews have been recently published, the present review will focus only on the most recent advances in the field, considering a new perspective of the endocannabinoid system as composed of both neuronal and glial divisions.

Keywords: Endocannabinoids; Receptors; Glia; Neuroinflammation

Contents

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1. Endocannabinoid neuronal system

1.1. CB_1 receptors

Since CB_1 receptors were first described on neuronal elements of the rat brain, a huge amount of in vivo and in vitro data has reinforced the assumption that the main functions of the endocannabinoid system (ECS) deal with the control of neuronal activity. Furthermore, many of the effects of exogenous and endogenous cannabinoids have been explained by the presence of these receptors in discrete neuronal circuits.

CB_1 receptor distribution in the rat brain is, by far, the best known among the different animal species studied. Autoradiographic (Herkenham et al., 1991), immunohistochemical (Tsou et al., 1998a), and in situ hybridization studies (Mailleux and Vanderhaeghen, 1992) have provided us with a detailed map of CB_1 localization in the rat CNS. Some striking features of these receptors include their atypical location during developmental stages (being present mostly in fiber-enriched areas) (Berrendero et al., 1998), together with their abundant and selective presence in discrete anatomical regions and neuronal circuits within the central nervous system (CNS), such as the cortex, hippocampal formation, basal ganglia, and cerebellum (Herkenham et al., 1991).

In all these structures, CB_1 receptors exhibit a presynaptic location, a feature that has served to hypothesize that the ECS could play a prominent role in synaptic neurotransmission. For instance, it has been involved in the control of the so-called "depolarization-induced suppression of inhibition" (DSI) and, more recently, of the "depolarization-induced suppression of excitation" (DSE) (for a recent review, see Alger, 2002). It is now accepted that endocannabinoids act as retrograde signaling molecules in these forms of short-term synaptic plasticity by activating CB_1 receptors, a fact that may have important consequences on reward and/or memory processes (Alger, 2002). Very recently, Mato et al. (2004) have shown that exogenous administration of delta-9-tetrahydrocannabinol ($^9\Delta$-THC) exerts a powerful CB_1-mediated influence on endocannabinoid retrograde signaling in the hippocampus and nucleus accumbens, which could partially explain some of the well-known behavioral effects of $^9\Delta$-THC. Recent data, however, point out that endocannabinoids may not be the only molecules enrolled in these pivotal regulatory events (Harkany et al., 2004).

The ECS is also involved in long-term regulation of synaptic plasticity. Data from different groups indicate that the ECS promotes homosynaptic and heterosynaptic long-term depression (LTD) in several areas of the rat brain such as the hippocampus, striatum, amygdala, and nucleus accumbens (Chevaleyre and Castillo, 2003; Hoffman et al., 2003). This action may be a crucial aspect on marijuana-induced alteration of memory, motor, and reward brain systems, respectively, and expands the physiological relevance of the ECS.

In addition, it must be noted that CB_1 activation may lead to different effects depending on the type of neuron where they are located. This has been specifically described in basal ganglia circuits, where neuronal populations differ in their phenotypic as well as in their electrophysiologic characteristics (Sanudo-Pena et al., 1999). For instance, apparently contradictory effects have been reported in striato-efferent neurons, as inhibition of GABA uptake as well as release have been documented (for review, see Romero et al., 2002b). Further, electrophysiological differences among striatoefferent GABAergic projecting neurons and subthalamonigral glutamatergic neurons are thought to support differences on the motor effects of cannabinoids at basal ganglia level (Sanudo-Pena et al., 1999; Romero et al., 2002b).

The putative postsynaptic location of CB_1 receptors as well as their possible functional roles are still highly debatable issues. In the past few years, several reports suggested that these receptors could exhibit a postsynaptic location in specific cell populations, such as pyramidal hippocampal neurons (Marsicano et al., 2003) and perivascular astrocytes (Rodriguez et al., 2001) in rat brain, and pars compacta dopaminergic neurons of the monkey mesencephalon (Ong and Mackie, 1999). Although other authors have provided convincing technical arguments against these data (Freund et al., 2003), possible interspecies differences cannot be ruled out, implying the need for additional work in this sense. The presence of CB_1 receptors on the postsynaptic side of the synaptic cleft would have important functional consequences related, for instance, to their known capability to modify the activity of several types of ion channels (reviewed in Howlett et al., 2002), thus participating in the control of action potential firing.

1.2. CB_2 receptors

Do neurons express CB_2 receptors? A few years ago, the answer would have been clearly "no." But recent evidence opens this field to new and appealing discussions. Thus, CB_2 receptors have been described in rat dorsal root ganglion (DRG) cultures and F-11 cells, a DRG X neuroblastoma hybridoma that displays several of the features of authentic DRG neurones (Ross et al., 2001). Very recently, Sokal et al. (2003) reported indirect evidence of the possible presence of CB_2 receptors on primary sensory neurones. Additionally, the presence of CB_2 receptors in granule and Purkinje cerebellar neurones of the mouse brain was shown by Skaper et al. (1996). These authors, however, raised the question of whether this expression was a consequence of the excitotoxic damage induced under their experimental conditions (Skaper et al., 1996). Preliminary evidence in human cerebellum shows that some neuronal cells may express this type of cannabinoid receptor (Núñez, Benito, Pazos, and Romero, unpublished observations). Taken together, these data point to the expression of a putative

CB_2 receptor on nervous cells. In any case, further experiments are needed to clarify the controversial existence of a neuronal subpopulation of "CB_2-like" receptors.

1.3. FAAH

Two degradative enzymes for endocannabinoids have been described so far: the fatty acid amide hydrolase (FAAH) and the monoacylglycerol lipase (MGL). It has been shown that the former is responsible for anandamide (AEA) degradation while the latter would act on 2-arachydonoylglycerol (2-AG) (Dinh et al., 2002a). The molecular characteristics as well as the tissular distribution of FAAH in different animal species are currently better known than those of MGL.

FAAH exhibits a wide distribution in the rat and human CNS. Large principal neurons (cortical and hippocampal pyramidal neurons, Purkinje cerebellar neurons, etc.) show high levels of FAAH expression (Romero et al., 2002a; Tsou et al., 1998b). Upon distribution studies, several aspects of the functional activity of FAAH are under consideration. First, it is important to note the postsynaptic localization of FAAH in different neuronal circuits, revealing a complementary pattern to that of CB_1 receptors (Egertova et al., 1998). The use of a variety of antibodies directed against different epitopes of FAAH protein seemed to corroborate this observation (Egertova et al., 1998; Tsou et al., 1998b). The question of how post-synaptic FAAH participates in AEA homeostasis control then arises as, according to current hypothesis on endocannabinoid retrograde signaling (see above), these same neurons would be the main producers of this endocannabinoid acting as retrograde messenger.

Furthermore, FAAH seems also to play a crucial role in the removal of AEA from the synaptic cleft. As well as occurring with other endogenous molecules that possess a neuromodulatory function, endocannabinoids have a specific system of inactivation. Endocannabinoids must be uptaken into cells and then suffer enzymatic hydrolysis. A carrier-mediated transport has been proposed, which differs from transport systems for classical neurotransmitters as it is neither dependent on external Na^+ ions nor affected by metabolic inhibitors. This feature suggests that it might be a carrier-facilitated diffusion process (Giuffrida et al., 2001).

However, the mechanism of endocannabinoids' entry into cells is not clear yet. It must be noted that an exciting controversy currently exists on the role of FAAH as the "driving force" of AEA uptake by neurons. Recent data from Glaser et al. (2003) suggest a prominent role for FAAH in AEA uptake in neuroblastoma and astrocytoma cells. On the contrary, Fegley et al. (2004) have recently shown that this process is indeed non-dependent on FAAH activity in mouse brain neurons, while Ligresti et al. (2004) have demonstrated that at least one protein different from FAAH is needed for AEA transport through the cell membrane. The critical point to be elucidated is obviously related to the possible existence of a specific uptake carrier for AEA. If such a protein would be characterized and cloned, the role of FAAH as well as a crucial aspect of the ECS "puzzle" would be resolved (for a recent review, see Hillard and Jarrahian, 2003).

Very recently, Ortega-Gutierrez et al. (2004) have provided new insights on this issue. Their results suggest the contribution of several mechanisms in AEA uptake by neurons: with the use of the specific AEA uptake blocker UCM707 in cell cultures of neurons from FAAH (−/−) and FAAH (+/+) mice, they distinguish FAAH-dependent and CB_1-dependent mechanisms as well as UCM707-dependent and UCM707-independent contributions. Notably, they estimate that around 30% of the total AEA uptake is carried out with the participation of a yet unknown cytosolic protein. These authors consider that AEA uptake may thus be the result of a concerted action of different mechanisms, with modest contributions of each of the players (Ortega-Gutierrez et al., 2004).

Little is known on the cellular distribution of MGL in the human CNS, due to the lack of specific antibodies for human MGL. To date, only data from rat brain have been published (Dinh et al., 2002b; Gulyas et al., 2004). Interestingly, FAAH and MGL distributions are highly complementary, with FAAH located on postsynaptic cell bodies and MGL on presynaptic structures. In light of immunohistochemical results, the authors of this study suggest putative differences in the homeostatic control of AEA and 2-AG by their corresponding degradative enzymes, with FAAH controlling AEA levels in the vicinity of its sites of synthesis and MGL participating in 2-AG degradation near its site of action (Gulyas et al., 2004).

1.4. Endocannabinoids

Di Marzo et al. (1994) were the first to describe the biosynthetic pathway for AEA in neurons. Afterwards, many papers have elucidated the synthetic and degradative pathways of the main endocannabinoids (for a review, see Di Marzo, this issue). Although isolated later (Mechoulam et al., 1995; Sugiura et al., 1995), 2-AG has become a target of increasing relevance. Its higher abundance in the CNS in respect to that of AEA, together with its ability to act as a full agonist of both CB_1 and CB_2 receptors, has led to several authors to postulate it as the true endogenous cannabinoid ligand (Sugiura et al., 2002).

Both AEA and 2-AG are not accumulated but released "on demand" immediately after they are synthesized. The molecular mechanism for their release is still unknown, although it has been suggested that it could be controlled by the same protein transporter involved in the uptake process (De Petrocellis et al., 2004).

Quantitative determination of endocannabinoids requires a rather complex technical approach. Fortunately, systems of high throughput and sensitivity are currently available (Walker et al., 1999). In addition, Felder et al. (1996) were

the first to report that a massive non-specific generation of endocannabinoids takes place shortly after death. Several authors further corroborated this point (Sugiura et al., 2001), which, together with the "on-demand" synthesis of the main endocannabinoids, may question data obtained in postmortem samples.

One of the most striking features of the ECS is that the high abundance of some of its elements is accompanied by extremely low levels of others. Thus, while the density of cannabinoid CB_1 receptors is very high in certain regions of the CNS, and they are counted among the most abundant receptors in the brain (reaching picomoles per milligram of protein in some regions of the rat brain; Herkenham et al., 1991), the amounts of endocannabinoids vary within the low femtomolar range (Walker et al., 1999). This contrasting difference could be explained by arguing that, as endocannabinoid action is limited to a very short distance range from their site of release (Freund et al., 2003), a massive presence of receptors should compensate that limitation.

Another point of controversy rises from the observation that CB_1 receptors seem to be coupled to their transduction mechanisms with low efficiency (Breivogel et al., 1997). This is even more evident if a comparative analysis with other types of G protein-coupled receptors is carried out (Sim et al., 1996). Interestingly, significant regional differences in the coupling efficiency of CB_1 receptors have been reported in rat brain. Even more, receptors located on brain areas that contain low amounts of CB_1 protein (i.e., thalamus, hypothalamus, etc.) seem to be more efficiently coupled to their signal transduction mechanisms than those located on CB_1-enriched regions (i.e., cerebellum, striatum, etc.) (Breivogel et al., 1997). The explanation for these differences is unknown, although it is highly suggestive of a selective regional functionality of the ECS in the brain.

On the other hand, neuroprotective properties of endocannabinoids have been described (Marsicano et al., 2003; Panikashvili et al., 2001). Thus, several reports have shown increases in AEA and/or 2-AG observed in different paradigms of brain injury, suggesting that such increases may be part of a "protecting" strategy (Mechoulam and Lichtman, 2003). In vitro studies seem to confirm this role of endocannabinoids, and point to the antiglutamatergic and pro-GABAergic properties of these compounds, together with the inhibition of calcium entry and the vasodilation induced by these compounds as the main mechanisms involved in these effects (Mechoulam et al., 2002), although vasoactive properties of cannabinoids may not participate in in vivo neuroprotection (Nagayama et al., 1999). Additionally, cannabinoid-induced hypothermia and anti-inflammation could also play a prominent role.

It must be noted that some of these effects are CB_1-mediated while others are not (Mechoulam et al., 2002). Further, the neuroprotective or neurotoxic properties of cannabinoids and, specifically, of endocannabinoids (Klegeris et al., 2003), seem to be related, among other factors, to the transformed vs. non-transformed nature of the cell line employed, respectively, in in vitro studies (for review, see Guzman et al., 2001; Guzman, 2003). Finally, it is also important to note that the blockade of CB_1 receptors has been reported to provide neuroprotection in certain experimental paradigms (Hansen et al., 2002). The explanation for this is far from being clear, but it is thought to deal with regional differences among the neuronal circuits implicated (Mechoulam and Lichtman, 2003).

2. Endocannabinoid glial system

Historically, glial cells were thought to play a rather "static" supporting role for neurons. However, there is growing evidence indicating that glial cells perform crucial functions in CNS homeostasis as well as under diverse pathological conditions (McGeer and McGeer, 1998). Specifically, the so-called "gliotic response" is an essential process that takes place after CNS insults and seems to dampen the devastating consequences of such lesions. However, if a chronic inflammatory process develops, viable cerebral tissues are damaged (Wyss-Coray and Mucke, 2002). As a result of these discoveries, neuroinflammation cannot be currently understood without the involvement of glial cells. It is then obviously of great importance to define the presence and function of the ECS in CNS glial cells.

2.1. CB_1 receptors

Glial cells express CB_1 receptors, although their precise role has been only partially unveiled. Astrocytes, microglia, and oligodendrocytes have been shown to express CB_1. Rodriguez et al. (2001) found CB_1 immunoreactivity in perisynaptic and perivascular astrocytes of the rat striatum, an observation concordant with in vitro data of astrocytes in culture, but not confirmed by other groups (Katona et al., 1999; Tsou et al., 1998a). Additionally, several reports have shown CB_1 expression by astrocytes in primary culture as well as by several astrocytoma cell lines (Guzman, 2003). It is important to note that CB_1 receptors have been reported to play a pivotal role on astrocytic cell death/survival decision, which, as stated before, may be different upon the transformed vs. non-transformed nature of the astrocytic cell line (Guzman, 2003).

Microglial cells in primary culture are also known to express this subtype of cannabinoid receptors. However, it seems that the well-described changes in microglial phenotype when in culture may also affect CB_1 receptors. Thus, it is not clear whether CB_1 presence in these cells is a consequence of their activation as there are no data regarding microglial CB_1 in vivo. Carrier et al. (2004) have recently shown that CB_1 receptors are expressed by a non-transformed rat microglia cell line. The functional significance of these receptors in microglia function is still

uncertain, although Waksman et al. (1999) proposed a prominent role for them in nitric oxide production, which is a crucial event in microglia-mediated neuroinflammation (Wyss-Coray and Mucke, 2002).

Of special physiological and therapeutic relevance may be the presence of CB_1 receptors on oligodendrocytes (Arevalo-Martin et al., 2003; Molina-Holgado et al., 2002). Using a rat model of multiple sclerosis, Arevalo-Martin et al. confirmed a possible relevant role for cannabinoids on the remyelination process after an inflammatory insult. In this promising effect, both CB_1 and CB_2 receptors seemed to be involved (Arevalo-Martin et al., 2003). These data have allowed these authors and others (Baker et al., 2001) to postulate the ECS as a possible relevant target for the development of new therapies for different diseases in which myelin sheath is affected, such as multiple sclerosis or amyotrophic lateral sclerosis.

2.2. CB_2 receptors

In vivo and in vitro studies showed that CB_2 receptors were present in cells related with the immune function. Among them are spleen macrophages, tonsils, B cells and natural killer cells, monocytes, neutrophils, and T cells (Galiegue et al., 1995). In addition, several groups reported on the presence of this receptor in in vitro cultures. Specifically, primary rat (Facchinetti et al., 2003), mouse (Walter et al., 2003), and human (Klegeris et al., 2003) microglia; and BV-2 (Walter et al., 2003), THP-1 (Klegeris et al., 2003), and RTMGL1 (Carrier et al., 2004) microglial cell lines have been shown to express CB_2 receptors. It must be taken into account that, as stated before, phenotypic changes due to culture conditions may take place and modify to some extent data obtained in primary microglial culture (Carrier et al., 2004). Although both pro- and anti-inflammatory effects derived from CB_2 activation have been documented (Carrier et al., 2004; Klegeris et al., 2003; Walter et al., 2003), it seems clear that CB_2 participates in crucial inflammatory events, such as microglial proliferation and/or migration.

Few studies have analysed the possible presence of CB_2 receptors in the CNS in vivo. Since their discovery, it has been thought that these receptors were located in cells of the immune system, but outside the CNS. In fact, molecular and autoradiographic studies showed that CB_2 receptors were absent in the mouse and rat CNS (for review, see Howlett et al., 2002). However, recent data obtained in our laboratory suggest that these receptors may be present in the human brain in normal as well as in pathologic conditions (Benito et al., 2003; Nunez et al., 2004). Specifically, microglia would be the unique glial cell type expressing CB_2 receptors in the human CNS.

In addition, only specific types of microglia seem to express CB_2 receptors in the human CNS. Immunohistochemical evidence indicate that, while perivascular macrophages are the only CB_2-positive glial cell in the non-pathologic human CNS, activated microglia seem also to be able to express this subtype of cannabinoid receptor in chronic degenerative processes. Specifically, tissue samples from Alzheimer's disease (AD) patients and from macaque brain affected by Simian Immunodeficiency Virus Encephalitis (SIVE) show strong immunoreactivity in macrophages and microglial cells. Further, these cells are located in the vicinity of the pathologic structures that are characteristic for each of these diseases (i.e., beta-amyloid-enriched neuritic plaques (in AD) and lymphoid infiltrates (in SIVE)) (Benito et al., 2003, 2005).

These data suggest that CB_2 might be involved in the neuroinflammatory process that develops in some forms of neurodegeneration. We speculate that these receptors, located on microglial activated cells, may modulate the release of different inflammatory mediators (Klegeris et al., 2003), as well as could influence proliferation (Carrier et al., 2004) and/or migration (Walter et al., 2003). Endogenous cannabinoids and, specifically 2-AG as full agonist of CB_2 receptors (Howlett et al., 2002), could act in a paracrine or even autocrine fashion to perform these functions.

It must be noticed, however, that new evidence supports the idea of a contribution of other still not fully characterized elements of the ECS in microglial function. Specifically, the possible role of the so-called "abnormal cannabidiol-sensitive receptor" (abn-CBDr) may be relevant. Pharmacological evidence suggest that this receptor might be involved in the control of migration of several cell types, among them microglia (Walter et al., 2003). Although this receptor has not been characterized at the molecular level yet, it may become a promising target for the modulation of inflammatory responses, as the main ligands for this receptor are devoid of psychoactive effects.

2.3. FAAH

We have previously reported that cortical and basal ganglia astrocytes express FAAH in the human brain (Romero et al., 2002a). Strikingly, studies performed in rat brain (Tsou et al., 1998b; Egertova et al., 1998) did not find glial expression of FAAH, which could reflect an inter-species variation in its expression pattern. As discussed above, FAAH may play a role in the synaptic regulation of the endocannabinoid transmission and its presence on astrocyte terminals could account for an additional regulatory function.

On the other hand, dramatical changes in FAAH expression have been recently described in AD tissue samples (Benito et al., 2003). FAAH appears to be overexpressed in astrocytes surrounding the beta amyloid-enriched neuritic plaques, which are one of the main pathological structures in AD. The significance of this observation is even greater considering two facts: (i) not only is the FAAH protein specially abundant in these hypertrophied astrocytes, but its enzymatic activity is also significantly higher; and (ii)

the presence of FAAH is limited to plaque-associated astrocytes, while it seems to be absent from other types of glial cells (i.e., microglia) (Benito et al., 2003).

Furthermore, expanding these studies to other pathological conditions, preliminary data obtained in our laboratory suggest that an identical pattern of selective overexpression of FAAH may occur in other neuroinflammatory processes. Thus, brain tissue samples from macaques with SIVE exhibit a marked FAAH immunoreactivity in astrocytes located in the vicinity of inflammatory infiltrates (Benito et al., 2005), which are one of the pathologic hallmarks of viral encephalitis (Kaul et al., 2001). It may thus be hypothesized that FAAH expression is increased in astrogliosis and that the ECS may be involved in the neuroinflammatory response, independently of the primary cause of such process.

It is important to note that one of the products of FAAH activity is arachidonic acid, which, in turn, is a precursor for other molecules that are important pro-inflammatory mediators (i.e., prostaglandins). In light of these data, it can be hypothesized that FAAH inhibition might be a new therapeutic approach in the treatment of neuroinflammation, as: (i) it would decrease the amount of arachidonic acid released in the proximity of the inflammatory focus; and (ii) it would allow AEA and, at least partially 2-AG, to activate cannabinoid receptors for longer periods of time. In this sense, the contribution of other endocannabinoid-degrading enzymes, such as MGL or, notably, type 2 cyclooxygenase (COX-2), should also be considered. Thus, it has been recently shown that COX-2 is able to metabolise AEA and 2-AG in vitro, and that the amounts of endocannabinoid derivatives generated in this pathway may be relevant, at least for some types of pro-inflammatory molecules (Kozak et al., 2002). Furthermore, COX-2 inhibition has been shown to potentiate the action of AEA and 2-AG, thus confirming a role for this enzyme in regulating endocannabinoids levels and activity (Kim and Alger, 2004).

2.4. Endocannabinoids

Recent data (Carrier et al., 2004; Walter et al., 2002) indicate that different types of glial cells are able to produce and release endocannabinoids in vitro. However, the physiological significance of this observation as well as the specific mechanisms of endocannabinoid production are still unknown. Remarkably, several groups have reported significant increases in endocannabinoids levels in different animal models of human disease, such as multiple sclerosis (Baker et al., 2001) or amyotrophic lateral sclerosis (Witting et al., 2004), in which glia is thought to play an important function. Furthermore, preliminary evidence suggests that

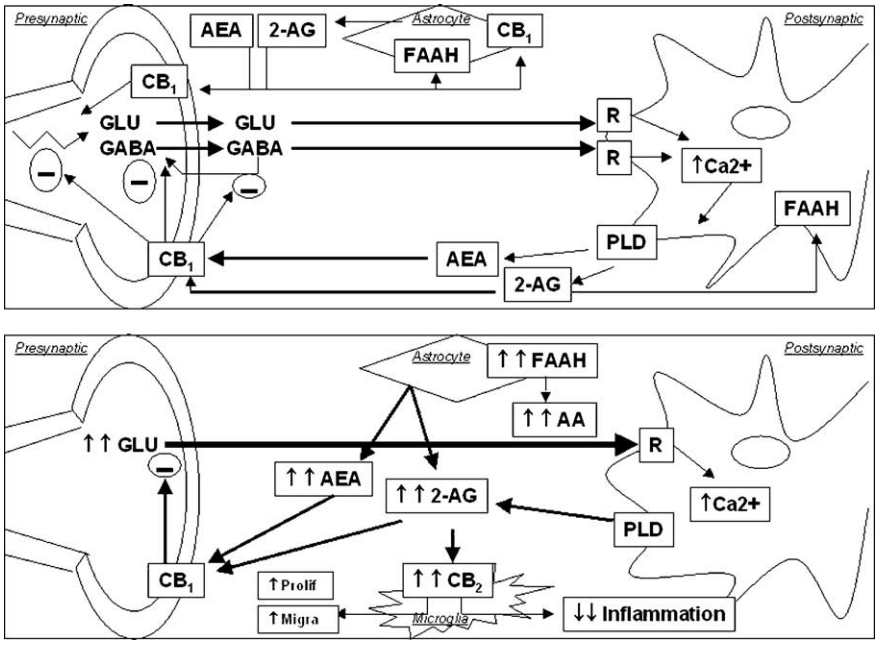

Fig. 1. Schematic representation of the main roles of the ECS under normal (upper panel) or pathologic (lower panel) conditions. Upper panel: in the healthy brain, the ECS plays important modulatory actions on neuronal activity, mainly inhibitory (decrease in neuronal excitability, neurotransmitter release, and uptake). An astrocytic component may be also involved. Lower panel: when an insult to the CNS occurs (especially when leading to an inflammatory reaction), excitoxicity induces neuronal damage and a "glial" ECS becomes up-regulated. Significant increases in endocannabinoids are observed. This glial ECS involves both astrocytes (FAAH overactivity, with putative increases in arachidonic acid (AA) generation) and microglia (with a prominent role for CB_2 receptors, although with somewhat contradictory results: decreases in the production of pro-inflammatory substances and, at the same time, triggering of microglia proliferation and migration). In addition, presynaptic CB_1-mediated inhibition of glutamate release partially counteracts excitotoxicity. PLD: phospholipase D.

endocannabinoid production by glial cells may underlie some of the neuroprotective properties of cannabinoids in experimental models of Huntington's and Parkinson's diseases (Lastres-Becker et al., 2005; J.J. Fernández-Ruiz, personal communication).

3. Conclusion

From what has been stated before, a novel perspective on the ECS functionality may arise. As depicted in Fig. 1, the functional neuroanatomy of the ECS in the normal, healthy brain seems to be quite different from that observed under pathological and, specifically, inflammatory conditions. Briefly, while CB_1 receptors and FAAH, together with the endocannabiods and their putative uptake mechanisms, play basic roles in the normal state, profound changes take place under inflammatory insults. Importantly, CB_2 expression seems to be induced in vivo in microglial cells, while FAAH is abundantly expressed in astroglia. In other words, it seems that a shift from the predominantly *neuronal* function of the ECS to a major *glial* participation occurs under pathological conditions (Fig. 1).

In summary, the ECS represents a promising and growing field of research. New data suggest that it may be an important element for the normal functioning of critical neuronal circuits of the CNS, as well as for the pathogenesis of a number of neurological diseases. Although still preliminary, a functional division between neuronal and glial elements of the ECS may be postulated, each having its own features, many of which are still to be characterized.

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