# Cannabinoids: Glutamatergic Transmission and Kynurenines

**Ana Laura Colín-González, Gabriela Aguilera, and Abel Santamaría**

**Abstract** The endocannabinoid system (ECS) comprises a complex of receptors, enzymes, and endogenous agonists that are widely distributed in the central nervous system of mammals and participates in a considerable number of neuromodulatory functions, including neurotransmission, immunological control, and cell signaling. In turn, the kynurenine pathway (KP) is the most relevant metabolic route for tryptophan degradation to form the metabolic precursor $NAD^+$. Recent studies demonstrate that the control exerted by the pharmacological manipulation of the ECS on the glutamatergic system in the brain may offer key information not only on the development of psychiatric disorders like psychosis and schizophrenia-like symptoms, but it also may constitute a solid basis for the development of therapeutic strategies to combat excitotoxic events occurring in neurological disorders like Huntington's disease (HD). Part of the evidence pointing to the last approach is based on experimental protocols demonstrating the efficacy of cannabinoids to prevent the deleterious actions of the endogenous neurotoxin and KP metabolite quinolinic acid (QUIN). These findings intuitively raise the question about what is the precise role of the ECS in tryptophan metabolism through KP and vice versa. In this chapter, we will review basic concepts on the physiology of both the ECS and the KP to finally describe those recent findings combining the components of these two systems and hypothesize the future course that the research in this emerging field will take in the next years.

**Keywords** Endocannabinoid system • Kynurenine pathway • Neuroactive metabolites • Neuromodulation • Cannabinoid receptors

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## Introduction

The history of humanity has been characterized by the use of natural resources to improve the health and life status. *Cannabis sativus* represented a medicinal alternative for different health problems before the twentieth century, but its use decayed later because of its recreational profile as an illicit drug (Robson 2014). Reconsideration of the use of cannabinoid-based medicine is growing recently due to an integral characterization of the endocannabinoid system (ECS) and its components, as well as the many physiological functions of which it seems to be responsible. It is precisely due to this increased interest for cannabinoid-based medicine that an intense search for cannabinoid drugs has grown up intensely during the last three decades (Sagredo et al. 2012).

Kynurenine pathway is probably the most important metabolic route for tryptophan (Tryp) degradation and synthesis of nicotinamide dinucleotide ($NAD^+$), a well-known metabolic precursor. This pathway consumes more than 90 % of the free Tryp and has been implicated in different physiological functions as well as in neurological and psychiatric disorders.

Herein, we offer an overview of both themes in order to offer new enlightening information about the present and the future of an emerging line of research combining these fields. We initiate with a general description of the ECS, to further follow with basic concepts of KP, and finally a description of those studies dealing with their interaction.

## Endocannabinoid System (ECS)

The ECS is formed by cannabinoid receptors, their ligands, and the enzymes involved in the endocannabinoid metabolism. The ECS regulates a wide range of functions in the CNS such as memory, blood pressure, cognition, movement, immunity, drug addiction, reproduction, sleep, and pain perception (Stella et al. 1997; Martin et al. 1999). Endocannabinoids release is triggered by calcium influx during depolarization or by activation of metabotropic glutamate receptors (mGluR1) and muscarinic acetylcholine receptors (mAChR) (El Manira et al. 2008).

### *Cannabinoid Receptors*

There are two well-characterized CB1 and CB2 receptors associated with GI/$G_o$-protein and other receptors less studied: G protein-coupled receptor 35 (GPR35), GPR55, peroxisome proliferator-activated receptors (PPARS), and the vanilloid transient receptor potential V1 (TRPV1) (Onaivi et al. 2012). CB1 is found mainly in the CNS while CB2 is located in peripheral tissues, especially in

the immune system (Galiegue et al. 1995; Onaivi 2009). CB1 is mostly located on GABAergic, glutamatergic, dopaminergic, noradrenergic, and serotonergic terminals (Morena et al. 2015).

## CB1 Receptor

CB1 is a G protein-coupled receptor whose gene is located on chromosome 6. Two types of $NH_2$ terminal splice variants have been reported. Several polymorphisms in the central cannabinoid receptor-1 (CNR1) gene have been described and their correlation with various neuropsychiatric features has been examined; some examples are mentioned in Table 1.

CB1 may exist as either a homodimer or heterodimer. The interaction of CB1 and D2 receptors was confirmed by co-immunoprecipitation and in vitro binding experiments. The complex can be formed by a direct protein-protein interaction mediated by the carboxyl terminus of CB1 and the third intracellular loop of the D2 receptor (Khan and Lee 2014). Orexin receptor 1 belongs to the superfamily of G protein-coupled receptors that overlap its distribution with CB1 in hippocampus and hypothalamus, exhibiting "crosstalk" interaction to modulate pain and feeding (Perrey et al. 2014; Ho et al. 2011; Crespo et al. 2008). CB1 also forms heterodimers with the μ-, κ-, δ-opioid receptors, the $A_{2A}$ adenosine receptors, and the $\beta_2$-adrenergic receptor (Hudson et al. 2010). The heterodimers formation of CB1 has been widely reported. However, their functional significance has yet to be fully understood.

**Table 1** Polymorphisms of the central cannabinoid receptor-1 (CNR1) gene and its correlation with various neuropsychiatric features

| Polymorphism | Effect | References |
|---|---|---|
| rs2023239 | Substance dependence | Hirvonen et al. (2013) |
| rs806378 | Tardive dyskinesia | Tiwari et al. (2012) |
| rs1535255, rs2023239, and rs1049353 | Impulsive behaviors | Ehlers et al. (2007) |
| CNR1 | Psychosis-related disorders<br>Metabolic disorders (obesity, hypercholesterolemia, and insulin resistance) | Eggan et al. (2008, 2012), Brown et al. (2014), Benzinou et al. (2008), Feng et al. (2010) |
| rs1049353 | Predisposition to the hebephrenic schizophrenia subtype | Ujike et al. (2002) |
| rs2501431 and rs1049353 | Depression | Monteleone et al. (2010), Mitjans et al. (2013) |
| rs12199654 and rs2023239 | Reduction in white matter volume | Onwuameze et al. (2013), Schacht et al. (2012) |
| rs1049353 | Reduction in caudate volume | Suárez-Pinilla et al. (2015) |
| rs2023239 | Reduction in thalamic volume<br>Schizophrenia | Suárez-Pinilla et al. (2015) |

CB1 is widely and richly expressed in the CNS, showing its major levels in the striatum, thalamus, hypothalamus, cerebellum, and lower brainstem. CB1 is mainly found in presynaptic elements of projecting neurons (Kano et al. 2009). Moreover, CB1 has also been located in the vesicular glutamate transporter (VGLUT)-1 protein, and in serotonin transporter in the mouse and rat frontal cortex (Ferreira et al. 2012), hence supporting an active role in neurotransmission.

### CB2 Receptor

Human CB2 is spliced to yield two isoforms CB2A and -B. CB2A is highly expressed in testis and shows some expression in the brain while CB2B is expressed in immune cells and tissues (Miller and Devi 2011). CB2 is expressed in microglial cells and is related to their activation state, as observed in macrophages. However, CB2 levels are higher in microglia than in macrophages. M2-type microglia (induced by IL-4 or IL-13) increase the synthesis of endocannabinoids and enhance the production of CB2, indicating that the signaling pathways associated with CB2 could be critical for the acquisition of an alternative phenotype in microglia (Mecha et al. 2015).

### TRPV1 Receptor

The transient receptor potential (TRP) family is a group of nonselective cation channels with a common structure of six transmembrane domains. There are six subfamilies of TRPs: canonical (TRPC1-7), vanilloid (TRPV1-6), melastatin (TRPM1-8), ankyrin (TRPA1), polycystin (TRPP1-3), mucolipin (TRPML1-3), and no-mechano-potential (TRPN). The vanilloid family is one of the best characterized subfamilies of TRP channels (Martins et al. 2014). TRPV1 receptor is a $Ca^{2+}$ channel activated by anandamide (AEA), but not by 2-2-arachidonoyl glycerol (2-AG), two well-known endocannabinoids. TRPV1 has anti-inflammatory and antinociceptive properties, and it has been related to behaviors such as fear, anxiety, stress, thermoregulation, pain, and synaptic plasticity (Edwards 2014).

### GPR55 Receptor

G protein-coupled receptor 55 (GPR55) induces intracellular calcium release via G 13/RhoA-mediated pathway. Similarly to GPR35, GPR55 is activated by AEA, virodhamine, cannabidiol, and lysophosphatidylinositols but not by WIN55, 212-2 (WIN), an agonist for CB1 and CB2 (Ryberg et al. 2007). GPR55 mRNA was found in the striatum, hippocampus, forebrain, cortex, and cerebellum (Wu et al. 2013). In the striatum, GPR55 heteromerizes with CB1 receptor and it has been suggested that it plays a role in motor coordination (Wu et al. 2013; Martínez-Pinilla et al. 2014).

## *Endocannabinoids*

Endocannabinoids are released lipids that activate cannabinoid receptors and are inactivated by uptake and hydrolysis. The ECS has two major endogenous ligands: AEA and 2-AG. They are synthesized "on demand" through $Ca^{2+}$-dependent and -independent mechanisms (Kano et al. 2009). AEA and 2-AG are present in peripheral and central tissues and their administration produces effects similar to those elicited by Δ9-tetrahydrocannabinol (THC) (Martin et al. 1999). Levels of 2-AG in the brain are >100 times greater than AEA (Stella et al. 1997).

In addition to the AEA and 2-AG, there are other active endocannabinoids such as dihomo-γ-linoleoyl ethanolamide, docosatetraenoyl ethanolamide, 2-arachidonyl glycerol ether, *O*-arachidonoylethanolamine, and *N*-arachidonoyldopamine (Kano et al. 2009).

## *Anandamide (AEA)*

### Biosynthesis

The synthesis of AEA occurs by several pathways. Liu and coworkers (2008) suggested that there are at least three pathways in which *N*-arachidonoyl phosphatidyl ethanolamine (NAPE) can be converted to AEA: (1) hydrolysis of NAPE by phospholipase D (NAPE-PLD); (2) deacylation of NAPE by α,β-hydrolase 4 (abhd4), a serine hydrolase, which serially removes acyl groups from NAPE to form lyso-NAPE and glycerophospho-arachidonoyl ethanolamide (GP-AEA). GP-AEA is subsequently hydrolyzed by metal-dependent phosphodiesterase (GDE1) and transformed into AEA; and (3) hydrolysis of NAPE by a type-C phospholipase which produces phosphoanandamide (pAEA), then an uncharacterized phosphatase dephosphorylates pAEA to form AEA (Liu et al. 2008; Okamoto et al. 2009). Degradation of AEA is performed by fatty acid amide hydrolase (FAAH), cyclooxygenase, and lipoxygenase (Kano et al. 2009).

### Physiological Effects

It was previously believed that the physiological effects of AEA were mediated only by CB1 and CB2 activation. However, several studies have now shown that AEA interacts with discrete binding sites on voltage-sensitive channels, producing wide-ranging effects on channel operation. Also, it has been demonstrated that AEA modulates voltage-gated $Ca^{2+}$ (Oz et al. 2000, 2005; Alptekin et al. 2010), $Na^{+}$ (Nicholson et al. 2003), and $K^{+}$ channels (review by Poling et al. 1996).

AEA directly inhibits the function of voltage-dependent calcium channels and alters the specific binding of calcium channel ligands, inhibiting neuronal $Ca^{2+}$ currents, and showing possible secondary effects on intracellular $Ca^{2+}$ homeostasis (Oz et al. 2000, 2005; Alptekin et al. 2010).

Nicholson et al. (2003) showed that AEA inhibits voltage-gated sodium channels in neuronal preparations. Therefore, AEA could work in the same way as class I antiarrhythmics, anticonvulsants, and anesthetics, which directly inhibit sodium channels (Nicholson et al. 2003; Al kury et al. 2014). AEA also inhibits the function of α subunits in neuronal sodium channels Nav1.2, Nav1.6, Nav1.7, and Nav1.8 (Okura et al. 2014). Thus, AEA may be used as a therapeutic tool in mechanisms related to inflammation and analgesia.

In addition, AEA interacts with voltage-gated $K^+$ channels in a cannabinoid receptor-independent manner. Moreno-Galindo and coworkers (2010) showed that AEA blocks ($IC_{50}$ = 200 nM) voltage-gated $K^+$ channels expressed on HEK-293 cells. AEA could interact with Val505 and Ile508 within the S6 domain, residues that form a hydrophobic motif important for the ion conduction pathway (Moreno-Galindo et al. 2010). By contrast, Barana et al. (2010) reported that AEA inhibits voltage-gated $K^+$ channels when it binds to the external vestibule. However, both reports showed that AEA blocks voltage-gated $K^+$ channels in a cannabinoid receptor-independent manner, acting as an intracellular messenger capable of modulating channel activity. The fact that AEA can act through cannabinoid receptor-independent manner suggests a direct chemical action of this molecule and a more complex pattern of actions for this cannabinoid, which is not merely related to its actions as an endogenous agonist.

Moreover, it has been demonstrated that AEA modulates the function of several other receptors: serotonin type 3 (Oz et al. 2002; Barann et al. 2002), nicotinic acetylcholine (Oz et al. 2003; Spivak et al. 2007; Butt et al. 2008), and glycine (Lozovaya et al. 2005; Hejazi et al. 2006), once again through a cannabinoid receptor-independent mechanism.

Intravenous administration of AEA increases extracellular dopamine levels in the nucleus accumbens, an effect that can be either cannabinoid receptor-dependent or -independent (Solinas et al. 2006). AEA modulates the activity of the dopamine transporter (DAT) through an unknown mechanism, producing this outcome, in part, by modulating DAT trafficking in a cannabinoid receptor-independent manner.

Age-dependent variations of the AEA have been shown. Under basal conditions, AEA levels, and NAPE-PLD and FAAH activities are higher in the hippocampus of mature (P56-70) compared to young rats (P14). Moreover, cannabinoid receptor binding increases in older rats (Fezza et al. 2014). These age-related brain changes may be related to an altered susceptibility and responsiveness in cerebral disorders.

The age-dependent changes of AEA levels modify the concentration of other endocannabinoids. There is a relationship between AEA and 2-AG concentrations. Higher AEA concentrations control the production of 2-AG by interaction with TRPV1 channels. In turn, the inhibition of AEA degradation reduces the levels, metabolism, and physiological effects of 2-AG (Maccarrone et al. 2008). Therefore, there is a tight correlation between AEA and 2-AG production. In contrast to this observation, a reduction of the AEA was found in the cerebrospinal fluid of patients affected by temporal lobe epilepsy compared with healthy control, whereas 2-AG levels were not affected; however, the role of this dysregulation still remains unclear (Romigi et al. 2010) and deserves detailed investigation.

## *2-Arachidonoyl Glycerol (2-AG)*

### Biosynthesis

The 2-AG synthesis began with phosphatidylinositol 4,5-biphosphate (PIP2) metabolism catalyzed by phospholipase C which triggers diacylglycerol (DAG) and inositol triphosphate (IP3). DAG is then converted into 2-AG by diacylglycerol lipase (DAGL). All forms of phospholipase C (σ, β, γ, ε, ζ, and η) require calcium for activation; therefore, the formation of 2-AG is calcium dependent (Stella et al. 1997). 2-AG is rapidly eliminated by intracellular serine hydrolases, principally by monoacylglycerol lipase (MAGL), and to a lesser degree by α, β-hydrolase-6 (ABDH6) and α, β-hydrolase-12 (ABDH12). These three enzymes have different subcellular localization (Navia-Paldanius et al. 2015). Degradation of 2-AG is also catalyzed by cyclooxygenase and lipoxygenase (Kano et al. 2009).

Previous studies have demonstrated a 2-AG levels increase in the adult brain exposed to various insults that triggers astrocyte stimulation and inflammation, which could be a neuroprotective mechanism (Fezza et al. 2014).

## *Cannabinoids are Retrograde Messengers*

Cannabinoids have the ability to mediate retrograde signaling in the brain via CB1 receptors, leading to reduced neuronal excitability. Cannabinoids are released from postsynaptic neuron and act on presynaptic CB receptors to decrease neurotransmitter release. However, cannabinoid signaling can also be CB receptor-independent involving voltage- and ligand-gated ion channels and the Cys-loop receptor superfamily (nicotinic, serotonin, and glycine) (for review see Oz 2006).

The interaction of endocannabinoids with their receptors decreases cyclic AMP levels, inhibits protein kinases A (PKA) activity, activates potassium channels, inhibits voltage-gated calcium channels, and suppresses transmitter release (Howlett et al. 2002). Below there is an explanation on how these molecules modify inhibitory and excitatory transmission using as example glycinergic and glutamatergic transmission.

### Modulation of Glycine Receptors

Glycinergic synaptic currents are presynaptically modulated through the retrograde cannabinoid signaling pathway. Cannabinoids exert dual concentration-dependent effects on glycine receptors. This modulation depends on the concentration of glycine; at low doses of glycine ($<EC_{30}$) cannabinoids augment glycine receptors current while at high concentrations ($>EC_{50}$) they suppress it (Lozovaya et al. 2011).

In the locomotor network, activation of postsynaptic mGluR1 induces release of endocannabinoids from both motoneurons and interneurons; in turn, the released endocannabinoids activate CB1 and cause decreased glycinergic transmission, which depress inhibitory synaptic transmission (Kettunen et al. 2005). Lozovaya et al. (2011) found that endocannabinoids can modulate postsynaptic glycinergic synaptic currents in Chinese hamster ovary cells that do not contain endogenous cannabinoid receptors. 2-AG, at physiological concentrations (0.1–1 μM), directly affects the function of recombinant homomeric glycine receptor, inhibiting peak amplitude and enhancing desensitization. These authors suggest that the receptor activity can be downregulated by progressive accumulation of the number of postsynaptic receptors being in a long-lasting desensitization state (Lozovaya et al. 2011). Thus, modulation of glycine receptor by endocannabinoids can be mediated by CB1-dependent and -independent mechanisms.

### Cannabinoids and Glutamatergic Synapses

AEA and WIN reversibly induced short-term depression of glutamatergic synapses on motoneurons by a CB1-dependent presynaptic mechanism. These CB receptor agonists reduced the available pool of synaptic vesicles at excitatory terminals. Cannabinoids may modulate glutamatergic transmission, incoming to neurons through the reduction in the probability of quantal release, action potential, and $Ca^{2+}$-dependent transmitter release (García-Morales et al. 2015).

To emphasize the relevance of CB1 for excitatory transmission, it was demonstrated that mice lacking CB1 in glutamatergic cells showed CA1 pyramidal neurons with increased branching and increased spine density in the apical dendritic region, indicating that the CB1 signaling exerted on excitatory neurons controls not only functional, but structural synaptic plasticity (Monory et al. 2015).

Chiarlone and coworkers (2014) found that only CB1 located in glutamatergic terminals plays an indispensable role in the neuroprotective activity of ECS. They suggested that intense activation of glutamatergic projection triggers the endocannabinoid synthesis on the glutamatergic terminal, inhibiting excess excitatory transmission and decreasing the neurotoxic effects produced by overactivation of NMDA receptors. Glutamatergic-induced excitotoxicity is one of the main mechanisms that mediated degeneration in many neurological diseases. Thus, endocannabinoids may be natural antiexcitotoxic agents with neuroprotective properties.

## *Neuroprotective Role of Cannabinoids*

Increased levels of cannabinoids can be reached by preventing their degradation, stimulating their synthesis, or increasing receptor binding. Pharmacology or genetic blockade of FAAH is the most used strategy in models of neurotoxicity. However, the precise molecular mechanism of neuroprotection is still unknown. For instance,

the administration of R (+) -WIN 55212-2 to animals decreases neuronal loss, infarct volume, and improves functional deficits and survival rates after cerebral ischemia via activation of CB1 (Nagayama et al. 1999; Hayakawa et al. 2009). Like this, several other examples of neuroprotective properties of cannabinoid agents are available in the literature. For practical purposes, we will discuss only those related to excitotoxicity and metabolites of the KP.

### The ECS and Huntington's Disease

Huntington's disease (HD) is an inheritable neurodegenerative disease affecting specific populations carrying the mutant huntingtin (mHtt) gene. This autosomal disorder is characterized by a polyQ expansion in mHtt, corticostriatal degeneration, alterations in glutamatergic and GABAergic transmission, excitotoxic events, choreiform movements, and dementia, among other hallmarks (Sagredo et al. 2012). It is the predictive nature of this neurodegenerative disorder that allows the design of therapeutic strategies. Recently, the use of Sativex™, a combination of THC- and cannabidiol-enriched botanical extracts, has recently emerged as a potential alternative for treatment of HD (Sagredo et al. 2012), since this cannabinoid-based design drug exhibits antihyperkinetic, anti-inflammatory, neuroprotective, and neuroregenerative properties at the preclinical level. These authors have addressed the issue of the initiation of clinical trials using this drug in HD patients. Since HD is a typical disorder coursing with excitotoxic events and alterations in the KP (Schwarcz et al. 2012), the use of cannabinoid-based medicine for this disorder prompts the detailed investigation on the mechanisms subordinated to the ECS that may alleviate the disease symptoms. Therefore, the ongoing clinical trials will provide important clues for the use of this therapeutic strategy against neurodegenerative events involving an altered glutamatergic transmission.

Given the relevance of the KP for the physiology and physiopathology in health status and neurodegenerative disorders, next we will briefly describe the most relevant points of this metabolic pathway.

## The Kynurenine Pathway

Among several metabolic routes in the brain and other tissues, the KP is the major cascade for the catabolism of tryptophan (Tryp), an essential amino acid (Jones and Brew 2013). The activity of this pathway is responsible for modulating endogenous levels of Tryp, thus influencing serotonin synthesis, a monoamine neurotransmitter which is synthesized from L-Tryp in a two-step mechanism. Overall, and most importantly, KP leads to the production of an essential pyrimidine nucleotide supply in mammals, the nicotinamide adenine dinucleotide ($NAD^+$), which ultimately plays a key role in cellular metabolism within the mitochondria. In addition, several metabolites with diverse neurological activities are formed throughout this cascade, all of which either participate in inflammation and immunoregulation processes or

exhibit pro/antiexcitotoxic properties. Such compounds include the metabolite L-kynurenine (KYN), the redox modulator 3-hydroxykynurenine (3-HK), the neuroprotectants picolinic acid (PA) and kynurenic acid (KYNA), and the excitotoxin quinolinic acid (QUIN) (Adams et al. 2014).

As depicted in Fig. 1, the catabolism of Tryp is carried out by indoleamine 2,3-dioxygenase 1 (IDO-1), 2,3-dioxygenase 2 (IDO-2), and tryptophan 2,3-dioxygenase (TDO) enzymes—yielding *N*-formylkynurenine (NFK)—all of which entails a rate-limiting step in the KYN synthesis. Independently, these two analogous heme dioxygenases catalyze the same reaction through what is thought to be a very similar mechanism, in order to deplete Tryp and achieve the formation of other KP metabolites. Expression of the monomeric enzyme IDO is constitutive and positively induced by several inflammatory stimuli (such as the release of the proinflammatory cytokine interferon-γ (IFN- γ), tumor necrosis factor (TNF), or lipopolysaccharide (LPS)). In turn, the tetrameric enzyme TDO is known to be expressed in the liver and its activity is upregulated by glucocorticoids and L-Tryp itself. KYN endures three distinct pathways in order to form KYNA, 3-HK, and anthranilic acid (AA). As such, NFK is degraded by a formamidase, yielding KYN, just to suffer irreversible transmission in both astrocytes and neurons by four different subtypes of kynurenine aminotransferases (KAT1 to KAT4), to ultimately form KYNA. Furthermore, kynurenine 3-monooxygenase (KMO) and kynureninase catalyze the degradation of KYN to 3-HK and

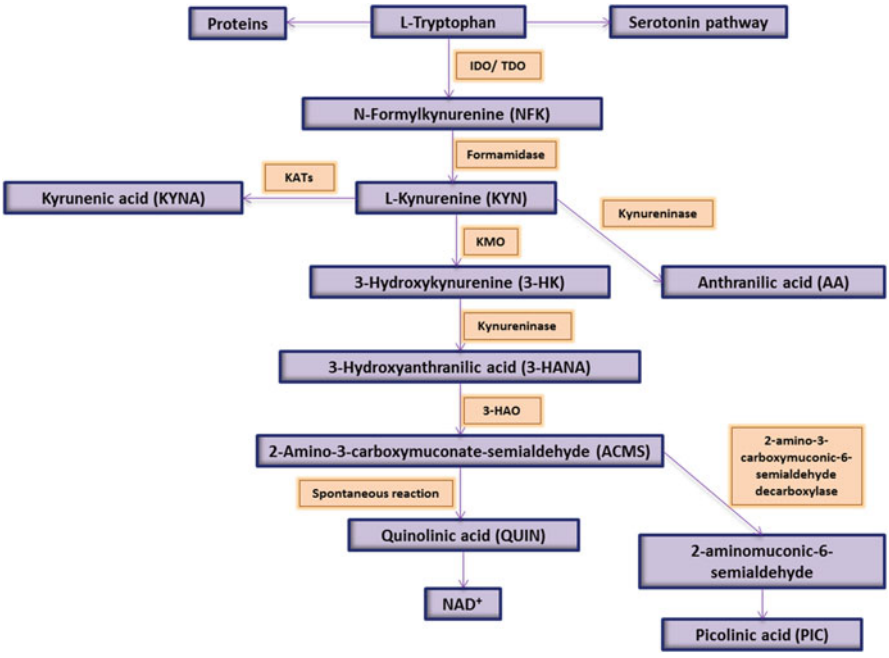


**Fig. 1** Complete tryptophan catabolism along the kynurenine pathway (KP)

AA. Then, the 2-amino-3-carboxymuconic-6-semialdehyde spontaneously rearranges to form QA under physiological conditions. In addition, very little amounts of 2-amino-3-carboxymuconic-6-semialdehyde decarboxylase are found in brain tissue, thus diminishing significantly the synthesis flow toward the production of PA. Finally, quinolinate phosphoribosyltransferase activity is remarkably low, and yet carries out the synthesis of $NAD^+$ (Schwarcz, et al. 2012; Vecsei et al. 2013; Adams et al. 2014; Ball et al. 2014; Yan et al. 2015). While under normal conditions KP runs to form $NAD^+$, under pathological conditions, such as inflammation, toxic metabolites accumulate in the brain.

## *Quinolinic Acid (QUIN) Synthesis*

To date, the QUIN-induced toxicity has been reviewed extensively, given that it is by far the most prominent neurotoxic metabolite in the KP. In accordance to its narrative profile, QUIN is an *N*-methyl-D-aspartate receptor (NMDAr) agonist often implicated in the pathogenesis of a number of human neurological diseases.

As a by-product of the oxidative metabolism of Tryp, QUIN is an important intermediate metabolite of the KP toward the production of $NAD^+$. However, taken as a whole, QUIN is vastly involved in several pathophysiological processes acting not only as a neurotoxin but also as a key molecule for the immune response. QUIN is found in nanomolar concentrations in the brain and cerebrospinal fluid, and examples of some of its most relevant targets include presynaptic receptors, oxidative stress, energetic dysfunction, and eventually cell death (Lugo-Huitrón et al. 2013). Consequently, this molecule, as a target, offers a number of potential therapeutic applications for modulators of both its synthesis and degradation processes.

Once kynurenine 3-hydroxylase is attained, 3-HK is produced from L-KYN; these steps constitute the most important subdivision in the whole QUIN synthesis, emphasized in Fig. 1. Under physiological conditions, KYN has been reported to mostly follow metabolism through hydroxylation (rather than the corresponding cleavage) due to a higher affinity, and therefore it metabolizes most of the KYN (Bender and McCreanor 1982). In addition, KYN is cleaved to produce 3-hydroxyanthranilic acid (3-HAA) by kynureninase, followed by catalysis of 3-HA to the aminocarboxymuconic semialdehyde, which rearranges to form QUIN by a nonenzymatic cyclization. Noteworthy, this intermediate can also produce PA, which exhibits protective properties against QUIN-induced toxicity to some extent (Bender and McCreanor 1982; Foster and Schwarcz 1986; Braidy et al. 2009; Costantino 2014).

### Toxic Mechanisms of QUIN

The mechanisms by which QUIN induces neurotoxicity have been extensively studied over the past decade. In agreement with what has been previously discussed, QUIN is an endogenous molecule that emerges as part of the Tryp catabolism, and

constitutes a glutamatergic agonist that acts on NMDAr. Under physiological conditions, QUIN is usually present in nanomolar concentrations in brain tissue and micromolar concentrations in cerebrospinal fluid (Pérez De La Cruz et al. 2012; Lugo-Huitrón et al. 2013), and is involved in the degradation of Tryp into $NAD^+$. However, pathological conditions are associated with its excitotoxic and pro-oxidant properties, which lead to increased concentrations of this metabolite accompanied by inflammatory stimuli (mainly evoked by cytokines); therefore, increased levels of QUIN are often linked with inflammatory responses in several disorders of the central nervous system (Chiarugi et al. 2000).

QUIN exerts its toxic pattern mainly through the overactivation of the NMDAr-ion channel complexes and endogenous glutamate, which in turn trigger strong deleterious events such as mitochondrial dysfunction induced by lysis-enzymes activation (and a consequent decrease in ATP levels), cytochrome C release (with the corresponding apoptosis set off), as well as oxidative stress. In addition, elevated levels of QUIN prompt the formation of reactive oxygen and nitrogen species (ROS and RNS, respectively), further yielding cells to oxidative damage. Overall, such processes finally lead to cell death by apoptotic or necrotic means. In agreement with these events, exposure to exogenous QUIN in experimental in vivo models, in particular in the striatum and cortex, is reported to cause neuronal cell death through excitotoxic mechanisms; interestingly, the toxic mechanisms induced by QUIN are not limited to neurons, but also affect glial cells, which raises attention toward the importance of determining neurological disorders that develop these circumstances (Chiarugi et al. 2000; Pérez-De La Cruz et al. 2012; Lugo-Huitrón et al. 2013). All of the above contribute to the general understanding of the excitotoxic mechanisms exerted by QUIN, as well as to appreciate the relevance of this by-product as a toxin associated with brain damage and the pathophysiology of diseases in the CNS.

## *Physiological Importance of KP*

The fact that Tryp constitutes the major source of the human body stores of $NAD^+$—a molecule involved in nearly all the biosynthetic metabolism—reveals the overall importance of KP and its link with several physiological events. In addition, aged metabolism itself alters the Tryp catabolism, all of which leads to a decreased nicotinamide biosynthesis over time (Reyes-Ocampo et al. 2014).

Among its numerous intermediates and by-products, the KP of Tryp catabolism involves two molecules exhibiting key neurobiological activities. On one hand, KYNA acts as an endogenous antagonist of glutamate and α-7-nicotinic acetylcholine receptors. On the other hand, QUIN has a well-defined NMDAr agonist activity (Cherian et al. 2014). Given this scenario, further studies and characterization of the elements downstream this cascade were, and remain, crucial when considering that excessive activation of the KP constitutes a consequence of inflammatory processes in a number of neurological diseases such as meningitis (Coutinho et al. 2014). Additional information supports this view, especially when taking into consideration that KYNA is strongly

related to embryonic brain development, in which alterations fall into severe consequences in neuronal morphology, structure, and activity up to maturity (Khalil et al. 2014). On the other hand, imbalances in the KP that enhance the production of KYNA instead of leading to the activation of the long arm of the pathway which is responsible for $NAD^+$ synthesis are proposed as part of the physiopathology of complex disorders such as schizophrenia (Kegel et al. 2014). Additionally, other elements of the KP have importance from a physiological point of view. For instance, the enzymes responsible for the Tryp degradation in the first steps of the cascade, IDO1, IDO2, and TDO, are accounted to restore antitumor immunity (van-Baren 2015). Also, as much as enzymes IDO1 and IDO2 are linked to Tryp catabolism and to several aspects of immune modulation, few information has been collected in regard to its specific role in physiological conditions, as well as its alterations in disease (Prendergast et al. 2014).

## *Role of KP in Neurodegenerative Diseases*

Regarding the aforementioned metabolites of the KP, whilst KYN and KYNA possess neuroprotective properties, 3-HAA and QUIN are, in general terms, considered as neurotoxic. Accordingly, considerable evidence supports the fact that KP has a role in normal physiology in the brain and is closely connected to the pathology of neurodegenerative diseases, such as Parkinson's disease (PD), Huntington's disease (HD), and others. In some reports, the genetic background was evaluated along the biochemical alterations of the KP; however, genetic elements such as single nucleotide polymorphisms (SNPs) have so far been ruled out of the hypothesis, reflecting that this might not influence the activity of some KP's intermediates (Torok et al. 2015). Up to date, it is known that during the development of inflammatory processes, KP catabolizes Tryp through several steps, in a mechanism that per se contributes to excitotoxic events through the release of QUIN and 3-HAA. Consequently, it is not surprising that such intermediates and products have been strongly related to the onset and development of neurological diseases that encompass degenerative factors. As examples, it is known that KP participates in the regulation of neuroinflammatory events in disorders such as Alzheimer's disease (AD) (Jones and Brew 2013). Moreover, the brain tissue of patients suffering neurological disorders such as schizophrenia often exhibits increased levels of KYNA, which is thought to contribute somewhat to the characteristic cognitive symptoms of such disorders (Cherian et al. 2014). Numerous approaches to the comprehension of QUIN toxicity also lead to important clues and insights on how an altered KP can be harmful. Oligodendrocyte cell lines have a limited threshold to QUIN catabolism in pathological concentrations and from an endogenous source, all of which emerges as an important hypothesis for encephalomyelitis and QA-induced gliotoxicity (Sundaram et al. 2014). Upon these circumstances, burgeoning research about the KP is currently providing new goals for the development of therapeutic approaches to explain and resolve neurodegenerative diseases with increasing incidence, including dementia, as well as disorders with severe impairment of motor and cognitive skills such as multiple sclerosis (MS). Unfortunately, despite the thorough

research that is conducted toward finding a neuroprotective strategy for this matter, the therapeutic approaches are still limited.

## The KP and the Endocannabinoid System: Demonstrated and Possible Interactions

Unexplainably, the role of kynurenines on the ECS and vice versa has been poorly explored this far. This is particularly intriguing since, as above mentioned: (1) KP produces at least two neuroactive metabolites with antagonistic profile one over the other (QUIN and KYNA), both acting at glutamate receptors and one of them also exerting modulation of cholinergic receptors; and (2) the ECS exerts intense modulation of neurotransmitter systems, especially on glutamatergic and GABAergic systems. Few reports have explored these interactions in a preliminary manner, constituting the basis for the upcoming studies. In this regard, probably one on the first reports providing key information on these two systems came from the study of Jenny and coworkers (2009). These authors presented evidence suggesting that the suppression of Tryp degradation by the cannabinoids Δ9-tetrahydrocannabinol or cannabidiol (at micromolar concentrations) via indoleamine-2,3-dioxygenase (IDO)—a mechanism that is independent of cannabinoid receptor activation—increased the availability of tryptophan for serotonin biosynthesis, thus contributing to enhance the ability of cannabinoids to improve mood disturbances. This effect is particularly relevant as it contrasts with the effects of the same cannabinoids at nanomolar concentrations, which, in a cannabinoid receptor-mediated mechanism, enhanced Tryp degradation in human blood mononuclear cells. Thus, there seem to be at least two mechanisms for cannabinoid action that might contribute to Tryp metabolism modulation, one related to a direct chemical action of these agents at micromolar ranges with no participation of cannabinoid receptors, and the other regulated by receptors, taking place at nanomolar ranges. From a physiological point of view, these findings are of major relevance as they open contrasting scenarios for the ECS and KP modulation.

In this section, we compile and update the advance on this field through the mention of those studies describing interactions between these two systems at the level of the two neuroactive KP metabolites: QUIN and KYNA.

### *Kynurenic Acid (KYNA) and Cannabinoids*

Unfortunately, most of the studies relating KYNA and the ECS have used the first more as a tool to evidence the role of glutamatergic transmission in different experimental protocols than a real target of the ECS. One of the few studies providing a physiological weight to KYNA after ECS manipulation established that silencing proinflammatory mediators will account for depletion of KYNA synthesis and further preservation of

learning and memory. In 2008, Andrade and coworkers explored the role of glutamatergic and lipid signaling in electroconvulsive therapy-induced retrograde amnesia in rats. Emphasis was paid on the involvement of cyclooxygenase (COX) mechanisms in amnesia, including the NMDAr and ECS systems. After testing different experimental conditions in animals receiving electroconvulsive shocks, the authors demonstrated that the electroconvulsive shock impairs cognition, upregulates the glutamatergic signaling, and generates excitotoxic conditions and hippocampal LTP, all through COX-2-mediated mechanisms involving the depletion of endogenous cannabinoids. The use of the COX-2 inhibitors indomethacin and celecoxib prevented these alterations presumably toward a mechanism partially involving the stimulation of the ECS and the consequent modulation of the glutamatergic system. In addition, while the COX-2-induced increase in the hippocampal levels of KYNA was assumed to compromise the glutamate-dependent NMDAr-mediated learning and memory processes, celecoxib inhibited KYNA synthesis, thus accounting for protection. Although this work did not establish specific interactions between KYNA and the ECS, it suggests for the first time that the modulation of the glutamatergic system and KP by the ECS could reduce the immunological reaction responsible for KYNA formation and further compromise the glutamatergic system. This evidence clearly points to a reduction of KP metabolism mediated by the ECS activation, which represents a topic deserving detailed investigation of further studies, as recently addressed by Hermann and Schneider (2012).

Further evidence on the involvement of CB1 in the modulation of neuronal activity in Substantia nigra pars compacta in rats through the modulation of receptors for excitatory amino acids was collected by Morera-Herreras and coworkers (2008). These authors employed KYNA to specifically test the involvement of NMDAr. Similar experiments conducted by the same authors demonstrated that CB1 activation modulates STN neuronal activity by mechanisms involving glutamatergic and GABAergic neurotransmission (Morera-Herreras et al. 2010). Simultaneously, Farkas and coworkers (2010) demonstrated that retrograde endocannabinoid signaling is capable of reducing GABAergic synaptic transmission to gonadotropin-releasing hormone neurons, emphasizing the suggestion that retrograde ECS signaling is crucial for the regulation of excitatory GABAergic inputs in hypothalamic neurons. Once again, KYNA was merely used as a tool to evidence the involvement of NMDAr-mediated excitatory events.

Interestingly, Zhao and Abood (2013) emphasized the fact that the G protein-coupled receptor GPR35, a protein involved in different physiological responses, including control of pain and inflammation, can act as a receptor for both KYNA and cannabinoids. In principle, this evidence suggests that the ECS and KYNA might, under certain circumstances, share physiological functions oriented to the modulation of the CNS. However, antagonistic actions of KYNA on the cannabinoid responses can be exerted upon other circumstances: recently, upon the concept that α-7-nicotinic acetylcholine receptors (a7nAChRs) modulate the effects of cannabinoids like THC, Justinova and coworkers (2013), carried out a series of experiments testing the effects of the 3-monooxygenase (KMO) inhibitor Ro 61-8048 on the brains levels of KYNA and the extracellular levels of dopamine induced by THC in a self-administration reward-related protocol. Ro 61-8048 augmented the KYNA

levels and reduced the extracellular content of dopamine, hence reducing the cannabinoid-dependent addictive behavior also in squirrel monkeys through a7nAChRs regulation. This important research opens interesting hypothesis about the relationship between KP and the cannabinoid axis, which requires detailed investigation upon both normal and pathological conditions.

## *Quinolinic Acid (QUIN) and Cannabinoids*

QUIN has been used as a tool to produce neurotoxic paradigms where the use of cannabinoids has been explored as potential therapeutic agents. In 2006, Pintor and coworkers used the toxic paradigm produced by QUIN as a model of HD in rats. The synthetic cannabinoid receptor agonist WIN 55,212-2 was tested as a protective tool to investigate the role of the ECS in this paradigm. WIN 55,212-2 dose dependently prevented the QUIN-induced glutamate release and reduced electrophysiological activity induced by QUIN in corticostriatal slices through a CB1-mediated mechanism. Under in vivo conditions, WIN 55,212-2 also prevented the striatal damage induced by QUIN. It was assumed that the stimulation of CB1 was responsible for the inhibition of glutamate release and the preventive actions observed in this study, which in turn could have therapeutic value as an approach to design strategies for HD and other neurodegenerative disorders.

Two years later, De March and coworkers (2008) addressed the issue of an involvement of CB1 in the upregulation of the gene transcription for the protective neurotrophin brain-derived neurotrophic factor (BDNF) in HD. They carried out experiments in rats lesioned with QUIN as the HD model to elucidate the relationship between cannabinoid receptors and BDNF upregulation. These authors found that after 2 weeks of progression of the striatal lesion induced by QUIN, cortical neurons projecting to the striatum contained more BDNF, which in turn coincided with an enhanced expression of CB1. These results were interpreted as a compensatory attempt of CB1 and the ECS to rescue striatal neurons in risk during excitotoxic events, emphasizing the relevance of the ECS as a first line of defense during degenerative events in the CNS. The faith of this early attempt certainly deserves more detailed investigation.

The studies described above established the protective role that CB1 stimulation can exert in the excitotoxic paradigm produced by QUIN; however, the role of CB2 located in glia remained unclear. Palazuelos and coworkers (2009) demonstrated that CB2 can also be neuroprotective against QUIN toxicity. These authors carried out experiments in which they found that CB2 expression was increased in microglia in HD patients and transgenic mouse models. While the genetic ablation of CB2 in the R6/2 transgenic mice stimulated the microglial activation leading to an aggravated HD symptomatology, and the striatal lesion with QUIN to CB2-deficient mice enhanced the nerve tissue damage and neuronal degeneration, microglial activation and inflammatory response, the induction of excitotoxic events with QUIN to wild-type animals administered with selective CB2 agonists prevented all toxic

endpoints. Interestingly, when astrocyte proliferation was selectively prevented in transgenic mice, it resulted clear that the observed CB2 actions were excluded from this population, hence leaving microglia as the cell type responsible for the protective actions of CB2. Therefore, CB2 can also account for an integral protective and a modulator profile of the ECS in neurodegenerative events.

Shortly thereafter, Casteels and coworkers (2010) monitored by PET the brain alterations in CB1 binding in the HD model produced by QUIN in rats in relation to glucose metabolism and D2 dopamine receptor upon the rationale that changes readily occur in the brains of HD patients. All these markers were decreased in the lesioned caudate-putamen. Changes in other brain regions were also detected. Based on their findings, the authors concluded that the changes in the ECS produced by QUIN comprised the caudate-putamen and other distant regions. Since both D2 and CB1 neurotransmission were found enhanced in the contralateral side, functional plasticity was proposed as a compensatory response. This work describes the changes occurring in the ECS during the progression of excitotoxic and neurodegenerative events in the brain and emphasizes the relevance of the ECS for the adequate physiological functioning of the CNS.

More recently, Sánchez-Blazquez and coworkers (2014) formally described in a review what it constitutes a key mechanism of action involving CB1 in the NMDAr-related schizophrenia, but that is also useful to explain neuroprotection mediated by CB1 under excitotoxic episodes. These authors established that, since the ECS controls $Ca^{2+}$ dynamics at the nerve terminal, there must be a physiological role exerted by the cannabinoid receptors to modulate the NMDAr activity, thus decreasing the response of the latter to excitatory stimuli. However, the use of cannabinoids to reduce the function of the glutamatergic system in neurological disorders remains under debate, given the diverse pharmacological properties that these agents exhibit, especially as psychostimulants. Indeed, frequent cannabis consumers have shown a high incidence of psychotic episodes, prompting symptoms of schizophrenia probably through the same mechanism inherent to neuromodulation and neuroprotection: reduction of NMDAr activity. In this regard, cannabinoids are supposed to exert these effects by two main mechanisms: (1) reduction of presynaptic glutamate release through presynaptic cannabinoid receptors, and/or (2) prevention of postsynaptic NMDAr-regulated signaling cascades induced by glutamate. While under normal conditions this modulation contributes to the preservation of homeostasis, under excitotoxic conditions like those prevailing in neurodegenerative disorders, this mechanism accounts for resistance to neurodegeneration; however, upon conditions of enhanced cannabinoid receptor stimulation, this modulation exerts a noxious number hypofunction. Thus, the association between cannabinoid receptors and NMDAr would be at the same time beneficial to prevent excitotoxicity and detrimental to induce schizophrenia-like psychosis. But how this interaction is supposed to act? The precise interaction between CB1 and NMDAr involves the NR1 subunit of the glutamatergic receptor: Once an endocannabinoid or a cannabinoid receptor agonist binds to its receptor, both postsynaptic CB1 C terminus and NR1 C1 segments located at the membrane surface interact through an arm of the histidine triad nucleotide-binding protein 1 (HINT1) homodimeric protein, as previously demonstrated by Vicente-Sánchez et al. (2013) and Sánchez-Blázquez et al. (2013). The complex formed by this interaction

(CB1-HINT1-NR1) is then internalized to be separated in the cytosolic space. While NR1 is submitted to proteasomal degradation, the re-sensitized CB1 returns to the membrane surface to reinitiate the cycle, finding another NR1 subunit to sequester it. This novel mechanism, presented in a summarized manner, represents an elegant explanation on how cannabinoid receptors—particularly CB1—reduce the bioavailability of NMDAr, hence decreasing the glutamatergic transmission with the subsequent positive or negative implications.

Another key contribution in this field has been released recently by Chiarlone and coworkers (2014). These authors addressed a major issue in regard to CB1, the most important G protein-coupled receptor in the mammalian brain. Since CB1 is expressed in both GABAergic and glutamatergic synapses, it is assumed that CB1 activation would be responsible for both excitatory and inhibitory responses. In order to establish the precise contribution of these receptors in neuroprotection, the authors explored their role in toxic models. First, QUIN was used as a tool to induce excitotoxic damage in the brain of mutant mice lacking CB1 in both GABAergic and glutamatergic neurons. In a second experimental protocol, the authors elegantly manipulated corticostriatal glutamatergic projections through a designer drug pharmacogenetic tool to evaluate the alterations in the R6/2 mouse model of HD that were either fully knocked out for CB1 or with a selective deletion of CB1 in corticostriatal glutamatergic or striatal GABAergic neurons. Their findings demonstrated that a restricted population of CB1 located in glutamatergic terminals contacting striatal neurons was in charge of the protective activity of the ECS, hence establishing them as potential therapeutic targets for neuroprotective paradigms. Through this approach, an important step has been given to characterize the neuroprotective profile that the ECS exerts in events involving excitotoxic damage, strongly linking the ECS with the glutamatergic system at specific levels. Immediately after this evidence appeared, our group made a new approach regarding the role of different cannabinoid agonists on the early pattern of toxicity elicited by QUIN in rat brain synaptosomes and striatal cultured cells (Rangel-López et al. 2015). Two synthetic (WIN 55,212-2 and CP 55,940) and one endogenous cannabinoid (anandamide or AEA) were tested as pretreatments in brain synaptic terminals and cultured striatal cells exposed to QUIN for a short time in order to provide key information on the timing and nature of toxic events occurring in the excitotoxic model and the role of the ECS in these early processes. While QUIN induced early loss of cell viability, mitochondrial dysfunction, and oxidative stress in these preparations, the three cannabinoid agents tested (WIN 55,212-2, CP 55-940, and AEA) prevented these effects, with WIN 55,212-2 being the most effective of all. Interestingly, the simultaneous incubation of cannabinoids with QUIN had no positive effects on toxic endpoints, suggesting that these agents shall exert their actions prior to the initiation of the excitotoxic event. Moreover, since WIN 55,212-2 prevented oxidative damage and mitochondrial dysfunction, it cannot be discarded at all that cannabinoid receptor agonists might induce preventive actions through mechanisms that are dependent or independent of cannabinoid receptors, an issue that deserves further detailed investigation.

However, at this point, a question is raised: Is there a real correlation between the ECS and the KP? So far, QUIN has been used merely as a tool to produce a neurodegenerative model with excitotoxic features, and so, the relationship should be considered unilateral, meaning that the ECS would be responsible for prevention mostly at the glutamatergic levels. On the other hand, the evidence showing that the ECS is affected in disorders like HD comprising changes in the KP cannot be ignored at all. Hence, it is true that this far this relationship has not been explored, or at least, it has not appeared reported elsewhere, but in regard to this topic, there is a clue that might help to hypothesize part of this interaction to enlighten the tendency of this relationship, independently of the trend that research will take on this topic: as previously mentioned, Jenny and coworkers (2009) showed that Tryp degradation is blocked by cannabinoids at micromolar concentrations through inhibition of IDO in a cannabinoid receptor-independent mechanism. If this effect inhibits KP, then it can be hypothesized that all metabolites would be decreased at these concentration ranges, whereas at nanomolar concentrations, cannabinoids increased Tryp degradation in human blood mononuclear cells in a cannabinoid receptor-dependent mechanism. Per se, these dual actions are highly suggestive of a possible adaptive modulatory action of the ECS on the KP metabolism; however, in order to validate this mechanism as an event with considerable relevance for the CNS, experimental evidence shall be collected reproducing these effects in brain cells and testing endogenous cannabinoid receptor agonists like AEA at different concentrations. This evidence is highly desirable to explain the many physiological and pathophysiological events that are attributable to the ECS in the human brain. Moreover, how cannabinoids reduce Tryp degradation in a receptor-independent manner? The first explanation for this effect would be linked to the action of other agents, some of which possess anti-inflammatory profiles, reducing the levels of cytokines that regulate IDO's activity. Examples of these agents are Norharmane (Chiarugi et al. 2000), alpha-methyltryptophan (Hou et al. 2007), rosmarinic acid (Lee et al. 2007), and some COX-2 inhibitors (Cesario and Rutella 2011). Detailed investigation is needed on the possible similarities, at the functional and chemical levels, of cannabinoids with all these agents. In addition, it cannot be discarded at all a direct action of cannabinoid agents at IDO or TDO, another branch for future studies. Finally, probably one of the most promising lines for future research is related to other direct actions of cannabinoids, as targets like oxidative stress and mitochondrial function would be revealing issues for the action of these agents. If besides all the mechanisms mentioned above are complemented with direct actions on these events, then the scope of action of these agents will grow up enough to consider new avenues of research with therapeutic perspectives.

## Concluding Remarks

The field of research devoted to the actions of cannabinoids at the central level, and more specifically at the neurotransmission level, is gaining attention every day as the ECS constitutes not only a widely distributed modulatory system but also an endogenous system in charge of neurotransmission and regulatory actions in

pathological disorders. The evidence presented in this chapter is intended to provide a wide scope of actions for the intervention and design of pharmacological therapies oriented to modulate the ECS at different levels. Indeed, we have learned from the collected and described evidence that cannabinoid agents are capable of exerting different actions, comprising mechanisms that are either dependent or independent of cannabinoid receptors. The fact that cannabinoid agonist can act through mechanisms not involving their receptors open new and exciting perspectives of research as their properties as protective, immunomodulatory, anti-inflammatory, and antioxidant, among several other properties, raise expectations on their selective use of experimental and clinical protocols. Furthermore, their selectiveness on specific neurotransmission systems, reducing glutamatergic transmission and regulating GABAergic and dopaminergic systems, contributes to their consideration for psychiatric and mood disorders. Most importantly is the possibility of using specific approaches based on the modification of the ECS to attend pathologies linked to alterations in the KP. In this regard, the immediate concept of employing these agents for the treatment of HD and other neurodegenerative disorders has found echo in reviews that offer recent evidence of selective cannabinoid drugs for this purpose. We have also learned recently from the depressive actions seen in Cannabis consumers, reaching the concept that a compromised glutamatergic transmission is also detrimental to humans, leading to schizophrenia-like symptoms. In summary, we are still quite far from understanding the complexity of this fascinating system and the many targets it comprises, but in the next year it is expected that we will collect key information on this topic.

**Compliance with Ethics Requirements** The authors declare that they have no conflicts of interest.

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