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REVIEW

Cannabinoids, TRPV and nitric oxide: the three ring circus of neuronal excitability

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Abstract

Endocannabinoid system is considered a relevant player in the regulation of neuronal excitability, since it contributes to maintaining the balance of the synaptic ionic milieu. Perturbations to bioelectric conductances have been implicated in the pathophysiological processes leading to hyperexcitability and epileptic seizures. Cannabinoid influence on neurosignalling is exerted on classic receptor-mediated mechanisms or on further molecular targets. Among these, transient receptor potential vanilloid (TRPV) are ionic channels modulated by cannabinoids that are involved in the transduction of a plethora of stimuli and trigger fundamental downstream pathways in the post-synaptic site. In this review, we aim at providing a brief summary of the most recent data about the cross-talk between cannabinoid system and TRPV channels, drawing attention on their role on neuronal hyperexcitability. Then, we aim to unveil a plausible point of interaction between these neural signalling systems taking into consideration nitric oxide, a gaseous molecule inducing profound modifications to neural performances. From this novel perspective, we struggle to propose innovative cellular mechanisms in the regulation of hyperexcitability phenomena, with the goal of exploring plausible CB-related mechanisms underpinning epileptic seizures.

Keywords Hippocampus · Endocannabinoids · TRPV · Nitric oxide · Hyperexcitability · Synaptic transmission

Abbreviations

2AG	2-Arachidonoylglycerol
7NI	7-Nitroindazole
ACEA	2′-Chloroethylamide
AEA	Anandamide
CA1	Cornus ammonis 1
CA3	Cornus ammonis 3
cAMP/PKA	Cyclic adenosine monophosphate/protein kinase A
CAP	Capsaicin
CB	Cannabinoid
CB_1R	Cannabinoid receptor type 1
CB_2R	Cannabinoid receptors type 2
CCK	Cholecystokinin
cGMP	Cyclic guanosine monophosphate
CNG	Cyclic nucleotide-gated
CNS	Central nervous system
CPZ	Capsazepine
DGLα	Diacylglycerol lipase α
DSE	Depolarization-induced suppression of excitation
DSI	Depolarization-induced suppression of inhibition
eCB	Endocannabinoids
EPSCs	Excitatory post-synaptic currents
FAAH	Fatty acid amide hydrolase enzyme
GLU	Glutamate
LTD	Long-term depression
LTP	Long-term potentiation
MDA	Maximal dentate gyrus activation
l-NAME	*N*-ω-nitro-L-arginine methyl ester
NO	Nitric oxide
NOS	NO synthase
nNOS	Neuronal NOS
eNOS	Endothelial NOS
iNOS	Inducible NOS
PKG	CGMP-dependent protein kinases
sGC	Soluble guanylyl cyclase
TLE	Temporal lobe epilepsy

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TRPV1	Transient receptor potential vanilloid type 1
VGCCs	Voltage-gated Ca^{2+} channels
WIN	(R)-(+)WIN 55,212-2

Introduction

Neuronal excitability and epilepsy

Endocannabinoid system (eCB) stands out for its variegated modulatory activity that physiologically influences central neuronal processes. eCB contributes to synaptic function by regulating processes such as memory formation, food intake, pain sensation, rewarded behaviour and neuronal excitability, though its exact role on neurosignalling is still to be fully unveiled (Ligresti et al. 2016).

Neuronal excitability is a basic feature of the nervous system, originating from the chemical and electrical gradients of its ionic milieu across cellular membrane. The mechanisms that maintain the ionic homeostasis constitute a major area of interest to understand how the central nervous system (CNS) controls excitability. If the excitability balance is abnormally altered, this can trigger hyperexcitability phenomena, eventually eliciting epileptic seizures (Navidhamidi et al. 2017). Seizures are paroxysmal phenomena due to abnormal, hypersynchronous discharge of specific populations of cortical neurons, above all in the hippocampus, a brain region particularly sensitive to the action of endogenous and exogoneous neuromodulators (Carletti et al. 2018; Gambino et al. 2018). Then, seizures eventually propagate to the entire cortex (Stafstrom and Carmant 2015). Epilepsy is defined as the clinical condition of recurrent, unprovoked seizures and epileptogenesis appears as the sequence of events turning a normal neuronal network into a hyperexcitable one (Bromfield et al. 2006).

Taking into account bioelectric activity, epileptic discharges occur in the parallel presence of high-frequency bursts of action potentials and hyper-synchronized neuronal population (Bromfield et al. 2006). At single-neuron level, the sustained, plateau-like neuronal depolarization that rapidly repolarizes and is followed by hyperpolarization create the "paroxysmal depolarizing shift" resulting in the burst of action potentials (Ayala et al. 1973). This prolonged depolarization of neuronal membranes is due to the influx of extracellular Ca^{++}, leading to the voltage-channel-mediated Na^{+} influx, that originates repetitive action potentials, and then the subsequent hyperpolarization is determined by GABA receptor-dependent Cl^{-} influx, or by K^{+} efflux. Paroxysmal activation can (a) increase extracellular K^{+}, attenuating hyperpolarizing outward K^{+} currents, (b) concentrate pre-synaptic Ca^{++}, enhancing neurotransmitter release, and (c) activate NMDA subtype of glutamate (GLU) excitatory receptors that sustains Ca^{++} influx and repetitive neuronal discharge (Bromfield et al. 2006). Loss of inhibitory control entails qualitative and quantitative changes in $GABA_A$ receptor subunits (Fritschy et al. 1999), modulation by other neurotransmitters (Chamberlain et al. 2012; Oliveira et al. 2010) and phenotypic changes of receptor subtypes from hyperpolarizing to depolarizing activity (Galanopoulou 2007).

The aim of this paper is to review the emerging and fascinating evidence highlighting the impact of eCBs on hyperexcitability, with a focus on innovative mechanisms of regulation. Initially, we briefly overview the pathophysiological role of cannabinoid (CB) receptors and of transient receptor potential vanilloid (TRPV) channels in the nervous system, with reference to neuroexcitability and epileptic seizures. Then, we summarise the current data about the mutual action of CB system and TRPV channels, drawing attention to TRPV as a putative novel receptor for cannabinoids. From this perspective, we finally discuss possible cellular mechanisms implied in CB-TRPV cross-talk in hyperexcitability taking into consideration the appealing role of nitric oxide. This interaction would open up pathophysiological perspectives extending knowledge on potential therapeutic relevance in epilepsy.

Cannabinoid modulation of neuronal hyperexcitability

Exploring the possible synaptic targets underlying the pathophysiological alterations of neural transmission could promote advancement in the knowledge of hyperexcitability phenomena. In this view, several key targets have attracted attention so far. Among these, eCB activity powerfully influences bioelectric balance via classic receptor-mediated mechanism or on further molecular players. The eCB system comprises neuroactive lipids and their two subtypes of receptors, cannabinoid receptor type 1 (CB_1R) and type 2 (CB_2R), widely distributed in the CNS and in the periphery (Storozhuk and Zholos 2018).

Endocannabinoid signalling in the brain

Endogenous cannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Ligresti et al. 2016) have been long considered to modulate neurotransmitter signalling exclusively via a retrograde, feedback mechanism. Their on-demand synthesis occurs in the post-synaptic terminal, after elevation of levels, by Ca-dependent synthesizing enzymes such as diacylglycerol lipase α (DGLα). After synaptic release, eCBs target pre-synaptic CB_1R or CB_2R coupled to the Gi/o proteins, triggering intracellular events by inhibition of either voltage-gated Ca^{2+} channels (VGCCs) or cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signalling (Howlett 2005; Wilson and Nicoll 2001).

In particular, pre-synaptic CB_1R can inhibit short-term plasticity mechanisms, in which CB_1Rs are activated for a few seconds, i.e.: the βγ subunits of G-proteins reduce pre-synaptic Ca^{2+} influx in the cytosol through VGCCs (Brown et al. 2003; Kreitzer and Regehr 2001; Wilson et al. 2001), whereas eCB-mediated long-term plasticity requires inhibition of adenylyl cyclase and down-regulation of the cAMP/PKA pathway (Castillo et al. 2012; Chevaleyre et al. 2006). Lastly, endogenous cannabinoids are metabolically deactivated after use by hydrolytic enzymes such as fatty acid amide hydrolase enzyme (FAAH) that degradates eCBs mainly in the post-synaptic site (Gulyas et al. 2004). In particular, this metabolizing enzyme rules the levels of AEA acting close to its cellular sites of synthesis, i.e. in proximity to Ca^{2+} stores in somata and dendrites of hippocampal principal cells, but not in interneurons (Gulyas et al. 2004). The eCBs are carried to the cytosolic localization of degradating enzymes; thanks to intracellular eCB transporters like fatty acid-binding proteins for anandamide (Gerra et al. 2010).

At the cortical level, CB_1R action on membrane conductance could be oriented towards the suppression of excitatory or inhibitory pre-synaptic neurotransmitter release, either regarding GLU or GABA release. These processes are known, respectively, as depolarization-induced suppression of excitation (DSE) or inhibition (DSI) (Kreitzer and Regehr 2001; Wilson and Nicoll 2001). In the hippocampus, the on-demand production of endocannabinoids from over-activated post-synaptic cells inhibits neurotransmitter release (Marsicano et al. 2003) specifically from two neuronal populations of CA1 area: cholecystokinin (CCK)-positive GABAergic interneurons and excitatory glutamatergic terminals onto pyramidal cells (Katona et al. 2006; Wilson and Nicoll 2001; Ferraro and Sardo 2009) (Fig. 1a). In accordance with this, CB_1R receptors can inhibit stimulus-evoked inhibitory or excitatory post-synaptic potentials (Castillo et al. 2012; Ohno-Shosaku et al. 2001; Wilson et al. 2001; Wilson and Nicoll 2001). As for the CB_2R, they are thought to act mainly on the peripheral nervous system and immune system, though recently discovered to engage in a variety of brain processes (Cabral et al. 2008; Castillo et al. 2012; Den Boon et al. 2012; Fernández-Ruiz et al. 2007; Morgan et al. 2009; Van Sickle et al. 2005).

Cannabinoid-mediated neuroprotection

All considered, CB receptors play a critical, neuroprotective part in a variety of pathological conditions connected to epilepsy. The neuroprotective effect exerted by CB_1R against excitotoxicity was primarily attributed to the inhibition of pre-synaptic glutamate release (Chiarlone et al. 2014; Shen

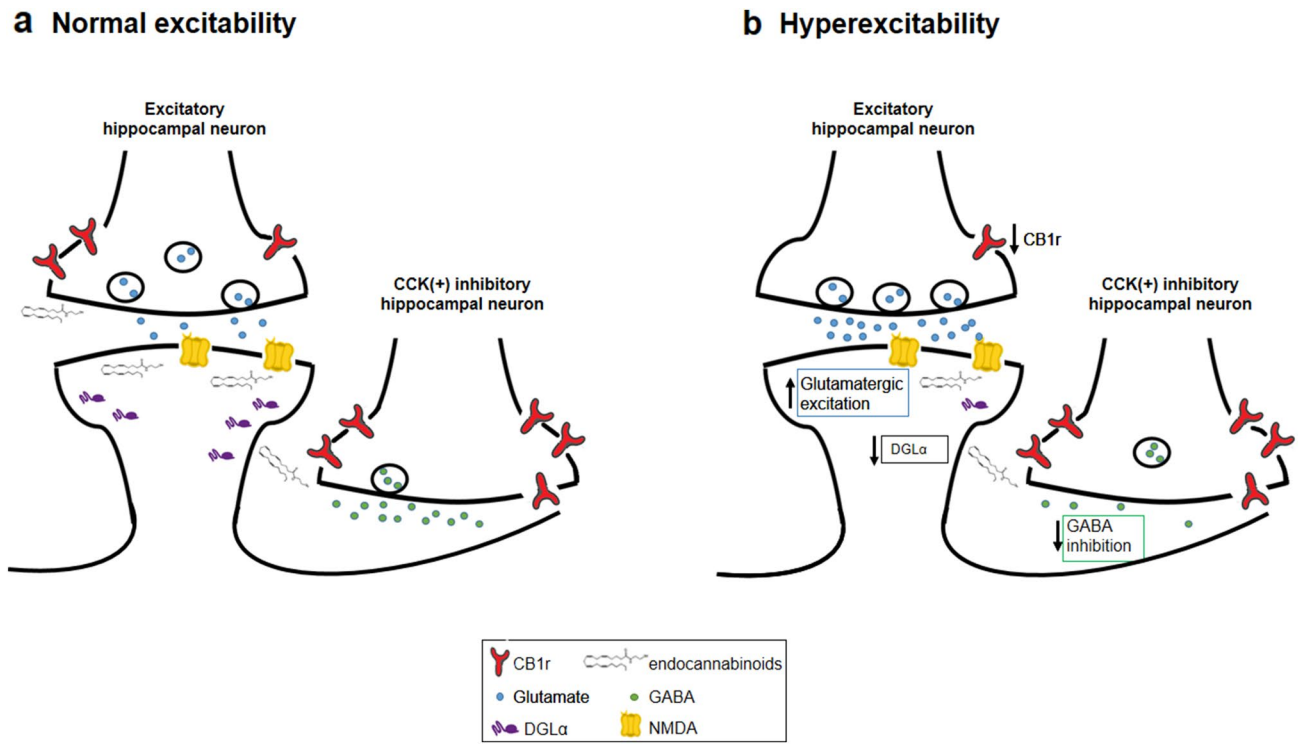

Fig. 1 Schematic representation of cannabinoid signalling in hippocampal synapses during normal excitability (**a**) versus hyperexcitability (**b**). In hyperexcitability phenomena, it was found a significant decrease in the expression of the cannabinoid synthesizing enzyme (DGLα) and of cannabinoid receptors (CB_1R) at hippocampal excitatory synapses, though CB_1R increases at axon terminals of cholecystokinin-positive (CCK+) interneurons. Overall, it was found an excessive glutamate transmission and reduced GABAergic inhibition

and Thayer 1999). Specifically, CB_1-mediated DSE has been hypothesized to be involved in the reduction of the seizure discharge in hippocampal cultures (Deshpande et al. 2007), supporting the hypothesis that the antiepileptic properties of CB agonists may be preferentially directed towards the inhibition of the GLU rather than GABA release (Monory et al. 2006). In the isolated hippocampus, a synthetic cannabinoid agonist (R)-(+) WIN 55,212-2 (hereafter, WIN) was found to reduce glutamate release from Schaffer's collaterals by interacting with CB_1 receptors (Németh et al. 2008). Several studies suggest that, in addition to the prominent inhibitory effects on Ca^{2+} influx and glutamate release, CB_1R-mediated neuroprotection can involve inhibition of nitric oxide (NO) production (Sánchez-Blázquez et al. 2013; Vicente-Sanchez et al. 2013).

Neuroprotection provided by cannabinoids was tested in several animal models of epilepsy indicating eCBs as endogenous antiepileptic agents in the brain (Hofmann and Frazier 2013; Monory et al. 2006). Indeed, activation of the CB_1R with endogenous and exogenous agonists inhibited electrophysiologically induced seizures in rats and in in vitro models (Blair et al. 2006; Rizzo et al. 2009; Wallace et al. 2001, 2003), whereas CB_1R antagonists prompted epileptic activity (Deshpande et al. 2007; Hofmann and Frazier 2013). Limited research was conducted on humans, showing that rimonabant (CB_1R antagonist) triggers paroxysmal events in epileptic patients (Braakman et al. 2009) and that a down-regulation of CB_1R and a reduced expression of DGLα can be encountered in human epileptic tissue (Ludányi et al. 2008). This may suggest that the neuroprotective endocannabinoid signalling pathway can be altered in severe chronic epilepsy (Fig. 1b) However, a biphasic effect of AEA at low and high doses emerged in various behavioural assays, besides well-reported anticonvulsant effects in animal models (Micale et al. 2009; Rubino et al. 2008). Such paradoxical effect of cannabinoids on epilepsy has been outlined in recent case reports on the use of the natural tetrahydrocannabidiol in patients (Armstrong et al. 2009; Cilio et al. 2014; Maa and Figi 2014; Soltesz et al. 2015) and in animal models as well (Sugaya and Kano 2018; Wallace et al. 2002). Hence, endogenous cannabinoids also have CB_1/CB_2R-independent mechanisms of action, beyond their receptor-mediated effects activating GLU transmission (De Petrocellis and Di Marzo 2009). An elegant study by Monory et al. (2015) further explored the dichotomy of cannabinoids in controlling both glutamatergic and GABAergic synapses to the purpose of regulating long-term potentiation (LTP) of synaptic transmission in the hippocampus. Their data revealed that CB_1R knock-out in cortical glutamatergic neurons improved LTP in the CA1, whilst CB_1R knock-out in forebrain GABAergic neurons reduced hippocampal LTP formation. This strengthens the idea of endocannabinoid system as a fundamental negative feedback maintaining homeostasis in the brain and could justify complex effects obtained by modulating this neuronal cascade.

Cannabinoids indeed directly modulate several voltage-gated channels (i.e. Ca^{2+}, Na^+ and various type of K^+ channels), ligand-gated ion channels (i.e. GABA, glycine), and ion-transporting membrane proteins such as TRPV channels. Considerable importance lies in TRPV amongst the novel molecular players involved in complex cannabinoid signalling. Nevertheless, exact mechanisms of cross-talk between TRPV and CBs are yet to be disclosed.

Role of TRPV channels on neuroexcitability

TRPV channels belong to a large superfamily of transmembrane ion channels modulating signal transduction in response to a myriad of chemical and physical stimuli. Among these channels, transient receptor potential vanilloid type 1 (TRPV1) is a polymodal, nonselective cation channel that is typically found in the plasma membrane and forms a passageway, allowing ions to cross the membrane upon activation (De Petrocellis et al. 2017; Muller et al. 2019).

TRPV1 brain localization and function

TRPV1 channels were initially discovered as thermal and pain sensors in peripheral tissues. They were later found not only in various brain areas, including thalamic and hypothalamic nuclei, locus ceruleus, periaqueductal grey, cerebellum, but also in cortical and limbic structures such as hippocampal formation (areas CA1, CA3 and dentate gyrus), central amygdala, caudate putamen and substantia nigra pars compacta (Cristino et al. 2006; Marsch et al. 2007; Mezey et al. 2000; Roberts et al. 2004; Starowicz et al. 2008; Toth et al. 2005). Subcellularly, TRPV1 expression has been found not only in cell bodies and synapses, predominantly on the post-synaptic dendritic spines of neurons, but also in synaptic vesicles and pre-synaptic nerve terminals of nucleus tractus solitarius, substantia nigra and dorsal root ganglion (Ho et al. 2012; Kauer and Gibson 2009; Toth et al. 2005). In the hippocampus, TRPV1 was found not only both in cell bodies of pyramidal neurons throughout the CA1 and CA3 regions and in the dentate gyrus, but also in the interneurons of stratum oriens-lacunosum-moleculare (Cristino et al. 2006; Hurtado-Zavala et al. 2017). Nevertheless, the observations of a widespread TRPV1 diffusion were contested by some authors restricting the CNS expression to the nociceptive sensory ganglia (Cavanaugh et al. 2011).

Over the last decade, TRPV1 has been implicated in a range of pathophysiological processes, because when gated, it induces a complex cascade of events: modulation of neuronal excitability, release of proinflammatory mediators, neurotoxicity and neurobehavioural development (Caterina

et al. 1997; Perchuk et al. 2019; Storozhuk and Zholos 2018). TRPV1 can be multi-modally activated by a number of endogenous and exogenous stimuli, including natural vanilloids (capsaicin and resiniferatoxin), heat, acids and arachidonic acid metabolites such as AEA (De Petrocellis et al. 2017). Endogenously produced lipids (identified as endovanilloids) activate TRPV1 family binding to the intracellular side of the channel, thus they are able to diffuse across plasma membrane or to be produced by the cell itself upon a signal. By presenting an intracellular binding site for AEA—the major endocannabinoid agonist—TRPV1 has been considered as a possible "ionotropic receptor counterpart" for CB_1R and CB_2R, since numerous pharmacological effects of AEA can be abolished by TRPV1 antagonism, knock-out and desensitization (Ligresti et al. 2016). AEA and capsaicin (CAP) share chemical and pharmacodynamic similarities as full agonists of TRPV1 (Szallasi and Blumberg 2007), whereas other cannabinoids, such as WIN and 2-arachidonoylglycerol (2-AG) cannot be considered as TRPV1 classical agonists, and their interference with this receptor is still to be uncovered (Di Marzo and De Petrocellis 2012). Noteworthy, the various stimuli gating TRPV1 are able to produce additive effects that can be integrated upon a specific signal.

TRPV1 and synaptic transmission

Focusing on synaptic transmission, it was underlined that TRPV1 augments the membrane permeability to Na^+ and Ca^{++}, thereby modulating neuronal excitability (Cristino et al. 2006; Menigoz and Boudes 2011; Saffarzadeh et al. 2015; Szallasi and Blumberg 2007). TRPV1, when localized pre-synaptically, enhances the frequency of glutamate-mediated spontaneous and miniature excitatory post-synaptic currents (EPSCs) in glutamatergic nerve terminals, whereas in GABAergic terminals, synaptic transmission appears unaffected (Derbenev et al. 2006; Li et al. 2004; Marinelli et al. 2002; 2003; Musella et al. 2009; Starowicz et al. 2007; Xing and Li 2007; Yang et al. 1998). This results in a potentiated synaptic transmission via increased glutamate release in an activity-dependent manner (Doyle et al. 2002; Kauer and Gibson 2009; Jin et al. 2004; Shoudai et al. 2010). Indeed, glutamate release evoked as eEPSCs is synchronous and mediated by Ca^{2+} influx via the activation of pre-synaptic VGCCs during action potentials (Yang 2016). In 2010, Peters and collegues added that synapses expressing the TRPV1 receptor upon afferent activation could also show a long-lasting asynchronous glutamate release that strongly potentiates the duration of post-synaptic spiking (Peters et al. 2010). Taken together, electrophysiological evidence supports that TRPV1, when activated, induces neuronal depolarization and contribute to generating action potentials that consequently facilitate the release of glutamate (Starowicz et al. 2007, 2008; Xing and Li 2007).

TRPV1 effect on hyperexcitability

TRPV1 is definitely implicated in excitatory mechanisms of synaptic plasticity (Fu et al. 2009; Gibson et al. 2008; Leite et al. 2005). In detail, evidence on the TRPV1 knock-out mice showed that LTP in CA1 of the dorsal hippocampus was reduced compared to TRPV1 activation (Marsch et al. 2007), as shown in other electrophysiological and behavioural studies in which CAP selectively activates LTP and reduce long-term depression (LTD) (Li et al. 2008; Manna and Umathe 2012). These effects are opposite to the ones of the TRPV1 full antagonist capsazepine (CPZ) (Messeguer et al. 2006). Also, Hurtado-Zavala et al. (2017) found that TRPV1 is expressed in the interneurons of the oriens-lacunosum-moleculare in the hippocampus. They identified TRPV1 as pivotal in regulating synaptic strength in as much as glutamatergic transmission is concerned, since the blockade of these channels has been related to an increased excitatory GLU innervation, presumably from CA1 pyramidal neurons. An engaging study by Gibson et al. (2008) pointed out that TRPV1, by inhibiting LTD in excitatory synapses selectively onto hippocampal interneurons and not on CA1, is expected to increase the excitability of innervated pyramidal cells. TRPV1 is thus differently distributed in hippocampal cells to selectively target inhibitory circuits. In any case, it seems that the signalling cascade for TRPV1-dependent regulation of synaptic efficiency is intrinsically linked to the eCB mediated (Chevaleyre et al. 2006; Kauer and Gibson 2009). Consequently, it is no surprise that TRPV1 agonist and antagonist, CAP and CPZ, have been studied in different models of epilepsy and produced opposite outcomes in the modification of neuronal firing (Bhaskaran and Smith 2010; Gonzalez-Reyes et al. 2013; Jia et al. 2015; Iannotti et al. 2014; Manna and Umathe 2012). Particularly, CAP was found to increase pathophysiological hippocampal firing in brain slices of mice in which epilepsy was induced by pilocarpine injection (Bhaskaran and Smith 2010). Pharmacological manipulation of TRPV1 receptor was performed in an in vivo rat model of hippocampal epilepsy developed by our lab, as in Carletti et al. (2013, 2016a). We revealed that systemic administration of CAP exerted a dose-dependent proepileptic effect on paroxysmal discharge in the dentate gyrus. These proepileptic effects were reverted by treatment with CPZ, though it did not induce any change alone. Interestingly enough, we showed that TRPV1 activation influences the antiepileptic action of the CB agonist WIN, by altering post-synaptic excitability levels (Carletti et al. 2016b). In agreement with our electrophysiological data, CAP and CPZ exerted, respectively, proepileptic and antiepileptic activity in several animal models of epileptogenesis

(Jia et al. 2015; Gonzalez-Reyes et al. 2013). As a case in point, Manna and Umathe (2012) reported opposite behavioural responses of intracerebroventricular (ICV) administration of CAP and CPZ in pentylenetetrazole-induced seizures in mice. To support TRPV1 role in hyperexcitability, recent immunohystochemical and immunofluorescence data on brains from patients with temporal lobe epilepsy (TLE) revealed an up-regulation of TRPV1 in temporal cortex and hippocampus (Sun et al. 2013). TRPV1-specific distribution was pointed out in cell bodies and dendrites of glutamatergic and GABAergic neurons, hinting at a possible alteration of the excitatory/inhibitory balance of neuronal circuits upon TRPV1 activation that could, therefore, be associated with epileptogenesis.

TRPV1 in the cannabinoid modulation of hyperexcitability

Endovanilloid transmission appears to be closely connected to endocannabinoid system in the regulation of neuronal excitability. To deepen knowledge on the controversial regulation of CB-TRPV1, we should take into consideration possible co-localization of CB_1 and TRPV1, as well as dynamic coordination by multiple factors of the efficacy and potency of endogenous and exogenous agonists of TRPV1.

Co-localization of post-synaptic TRPV1 and pre-synaptic CB_1R

Anatomical evidence indeed demonstrated the co-localization of TRPV1 and CB_1 within several brain structures (Cristino et al. 2006; Micale et al. 2009). Especially in the hippocampal formation, they are closely expressed in the synaptic cleft: CB_1 were primarily found in axon terminals and TRPV1 in post-synaptic dendritic spines and cell somata (Cristino et al. 2006; Toth et al. 2005; Wilson and Nicoll 2001). CB_1-activation normally leads to a Ca^{2+}-dependent reduction in transmitter release from pre-synaptic terminals (Freund et al. 2003; Mackie and Hille 1992), whereas TRPV1 gated by AEA, promotes Ca^{2+} influx in post-synaptic sites (van der Stelt and Di Marzo 2005). Endovanilloids, if synthetised outside the cell, will primarily trigger CB_1 and then cytosolic TRPV1 upon cellular reuptake, whereas if produced within the neuron, they will stimulate TRPV1 at first (Adermark and Lovinger 2007; Hillard and Jarrahian 2005). The complex regulation exerted by AEA on CB_1R and TRPV1 could be detailed as follows: on one hand, CB_1R pre-synaptic activation by AEA constitutively maintains TRPV1 in a sensitized state and responsive to capsaicin (Fioravanti et al. 2008). On the other hand, TRPV1 post-synaptic activation by AEA is able to hyperpolarize neurons reducing 2AG biosynthesis by DAGLα, ultimately counteracting CB_1-mediated inhibition of GABA release (Maccarrone et al. 2008; Musella et al. 2010). Also, anandamide acting on post-synaptic TRPV1 can suppress excitatory transmission in the dentate gyrus by modulating metabotropic glutamate receptors via stimulation of AMPA and mGluR5 internalization (Chavez et al. 2010). This gave rise to the idea that TRPV1 and CB_1 might exert opposite effects on neuronal signalling and several pathophysiological processes, remarkably on epilepsy (De Petrocellis and Di Marzo 2010).

Pre-synaptic co-localization of TRPV1 and CB_1R

Nevertheless, TRPV1–CB_1R functional cross-talk appears even more intriguing, since TRPV1 and CB_1 can also be both expressed pre-synaptically (De Petrocellis and Di Marzo 2009). In that case, CB_1 activation can alter membrane potential via VGCCs and K^+ channels, thereby influencing voltage-gated TRPV1 opening. Conversely, TRPV1 influences intracellular Ca^{2+} concentration, thus it could inhibit CB_1-dependent VGCCs (Wu et al. 2005). Additionally, the signalling cascade for TRPV1-dependent regulation of synaptic efficiency is intimately related to the eCB mediated (Chevaleyre et al. 2006), in which post-synaptic metabotropic glutamate receptors could trigger production of retrograde lipid messengers acting on a pre-synaptic target (Kauer and Gibson 2009).

Post-synaptic co-localization of TRPV1 and CB_1R

It is also possible that CB_1 and TRPV1 could be both located post-synaptically and consequently, TRPV1 channels have gained importance as main target of eCB non-retrograde signalling, which requires that eCBs produced in post-synaptic terminals activate post-synaptic CB_1R or TRPV1 (Castillo et al. 2012). In this context, synaptic efficiency is affected by a post-synaptic form of LTD mediated by TRPV1 and activated by AEA, which differs from the pre-synaptic, TRPV1-dependent LTD at glutamatergic synapses onto CA1 hippocampal interneurons (Gibson et al. 2008). The post-synaptic TRPV1-LTD has been observed in dentate granule cells and other cortical areas (Chavez et al. 2010; Grueter et al. 2010; Puente et al. 2011). Non-retrograde eCB signalling has been considered as a main target for neuronal excitability in other contexts such as CB_1R-dependent self-inhibition in post-synaptic sites in neocortical interneurons, pyramidal and CA1 neurons (Bacci et al. 2004; Marinelli et al. 2008, 2009; Min et al. 2010). In particular, CB_1R-dependent post-synaptic hyperpolarization after repetitive stimulation reduced excitability of neocortical GABAergic interneurons (Bacci et al. 2004). This slow self-inhibition resulted from activity-dependent rises in intracellular Ca^{2+}, mobilization of 2AG, and activation of

CB_1Rs that couple to a G-protein-activated inwardly rectifying K^+ channel (Bacci et al. 2004; Marinelli et al. 2008, 2009). Remarkably, in the hippocampus, it was hypothesized by Yang et al. (2013) that the action of cannabinoids such as WIN is utter enough when exerted on CB_1 and TRPV1 post-synaptically co-localized, therefore, subject to a protein–protein interaction that can decline depolarizing currents, eventually suppressing TRPV1 downstream events. TRPV1 was also discovered in neuronal intracellular compartments such as the endoplasmic reticulum, trans-Golgi network, and vesicles (Dong et al. 2010), in agreement with the hypothesis that AEA can act as an intracellular messenger too (van der Stelt and Di Marzo 2005).

TRPV1 and CB_1R cross-talk in hyperexcitability

The pharmacological application of endocannabinoids and endovanilloids, such as anandamide or capsaicin is effective on TRPV1 activity in epilepsy models and is challenged both by CB_1 and by TRPV1 antagonists such as CPZ (Bhaskaran and Smith 2010; Chavez et al. 2010; Di Marzo and De Petrocellis 2012; Manna and Umathe 2012). One of the first studies employing systemic administrations of TRPV1–CB-active drugs on in vivo rat models of hyperexcitability was published by our lab (Carletti et al. 2016b). We assessed the outcomes of a pharmacological manipulation of TRPV1–CB_1 signalling, applying CAP, CPZ and WIN in an in vivo rat model of TLE, in the context of the reverberant hippocampal–parahippocampal circuitry (Banach et al. 2011; Sardo et al. 2006). To this purpose, we exploited an electrically induced acute model of epilepsy, the maximal dentate activation (MDA) that was already employed to draw attention to the antiepileptic effect of WIN and the interplay of cannabinoids with other cellular signalling systems (Carletti et al. 2015; Rizzo et al. 2009, 2014). The coincident CB_1 activation and TRPV1 antagonism facilitated antiepileptic outcomes, as well as TRPV1 agonism interferes with CB_1-mediated neuroprotection in hyperexcitability, though the exact molecular mechanism implicated deserves deeper investigations. Dephosphorylation and desensitization of TRPV1 channels were included among the potential mechanisms of action of cannabinoids on the post-synaptic side (Iannotti et al. 2014; Nazıroğlu 2015; Lupica et al. 2017; Yang et al. 2013). All the reported findings have surely established a novel paradigm for the existence of TRPV1 molecular targets of cannabinoids via the modulation of complex inhibitory pathways in the post-synaptic site, which could contribute to reducing excitability levels in pathophysiological processes (Castillo et al. 2012; Hong et al. 2009; Wang et al. 2012). Among the possible intracellular molecules implicated in CB-TRPV1 pathway, nitric oxide emerged as a still unexplored point of interaction.

Nitric oxide: a plausible point of interaction?

Synaptic localization and activity of nitric oxide

NO is a gaseous molecule whose distribution of synthetic and signal transduction machinery is wide enough to serve various functions in the CNS, as well as performing a neurotransmitter-like role in the periphery (Garthwaite 2008).

Three different isoforms of NO synthase (NOS) produce NO from the oxidation of L-arginine in the brain. The calcium-activated neuronal (nNOS) and endothelial (eNOS) are constitutive isoforms: the first is generally found in central and peripheral nervous system, localizing in synaptic spines, and is preferentially inhibited by 7-nitroindazole (7NI); the second is expressed in endothelial brain tissue and astrocytes in particular. Instead, the Ca^{2+}-independent isoform (iNOS) is inducible and can be expressed by macrophages and in microglia upon immunological challenge (Garthwaite 2008; Yoshino et al. 2017; Zhou and Zhu 2009). Specifically, nNOS has been described in various brain regions (cortex, hypothalamus, dorsal raphe, amygdala and others; Zhou et al. 2018). Above all, it is expressed in several sub-regions of the hippocampus, e.g. dentate gurus, hilus, CA3, CA1 and subiculum, in different cell types such as interneurons, granular neurons and pyramidal neurons (Zhou et al. 2018).

NO is predominantly produced post-synaptically in many brain circuits, though it can also derive from presynaptic axon terminals, similar to peripheral nitrergic nerves (Garthwaite 2008; Toda and Herman 2005). Its main effector is the soluble guanylyl cyclase (sGC), a cGMP-producing enzyme (Feil and Kleppisch 2008), downstream acting on cGMP-dependent protein kinases (PKG) or cyclic nucleotide-gated (CNG) ion channels that ultimately reduce intracellular Ca^{2+}. At molecular level, NO can impact on voltage-gated and ligand-gated channels either switching on the classical cGMP pathway or through protein modification (Garthwaite 2008; Kiss 2000), for example interfering with nuclear transcription, epigenetics, CAPON coupling and mTOR (Itzhak et al. 2014; Harraz and Snyder 2017; Zhou et al. 2018; Zhu et al. 2014).

Furthermore, NO acts via Ca^{2+}-dependent and -independent processes affecting the release of neurotransmitters and numerous neurosignalling systems, i.e. glutamate, GABA, acetylcholine, dopamine, noradrenaline and serotonin (Arancio et al. 1995; Cai et al. 2019; Ohkuma and Katsura 2001) (Fig. 2). NO is then degradated by reacting with other naturally present chemical species in the cell, for instance, haemoglobin in circulating erythrocites (Liu et al. 1998).

Upon a mechanistic viewpoint, nitrergic signalling appears, therefore, to act as one of the more conventional

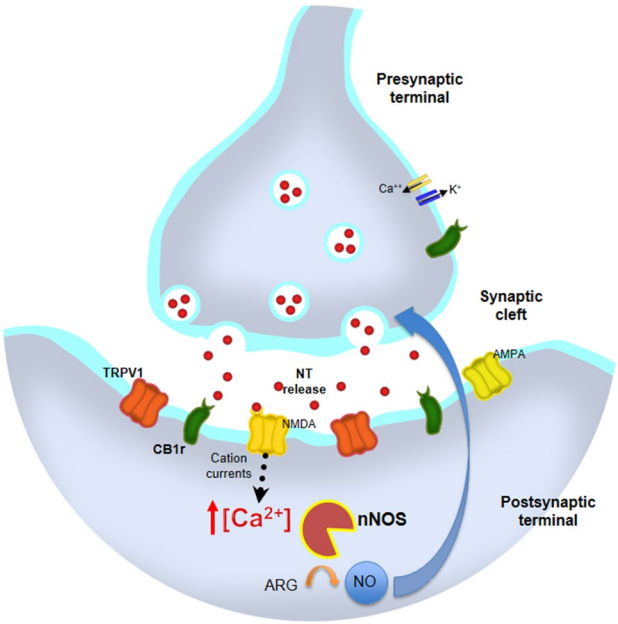

Fig. 2 In hippocampal synapses, the release of glutamate (depicted as dots in the synaptic cleft) activates NMDA-mediated cation currents in the post-synaptic terminal that elevate intracellular calcium (Ca^{2+}). This activates neuronal nitric oxide synthase (nNOS) producing nitric oxide (NO) from L-arginine (ARG) and sustains further NO-mediated pre-synaptic release of glutamate

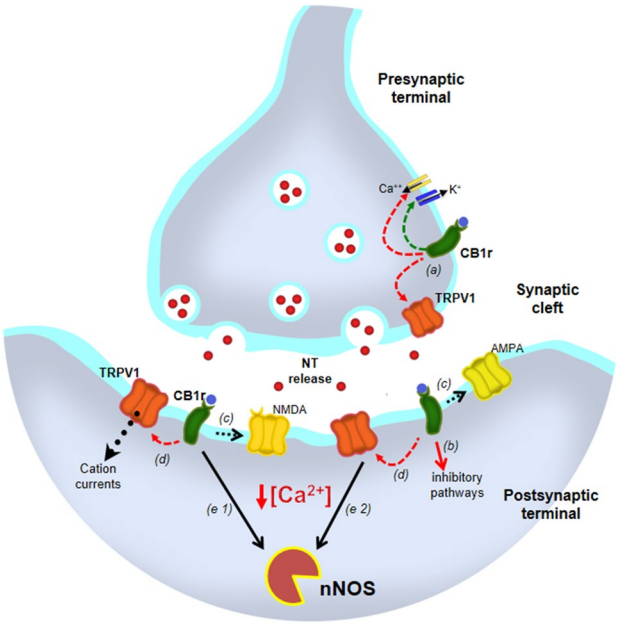

Fig. 3 Cannabinoid control on hippocampal neurotransmission in hyperexcitability states could be due to **a** reduced release of pre-synaptic glutamate or other neurotransmitters (NT; depicted as dots in the synaptic cleft) via modulation (indicated by dashed arrows →) of currents mediated by Ca^{2+}, K^+ and pre-synaptic TRPV1 by CB_1 receptors. **b** triggering of complex inhibitory pathways via post-synaptic CB_1 receptors (indicated with a continue arrow →). **c** decreasing intracellular Ca^{2+} concentration in the post-synaptic site via direct regulation of NMDA and AMPA channels (indicated with spotted arrows) via post-synaptic CB_1 receptors. **d** modulation (indicated with a dashed arrow →) of TRPV1-mediated post-synaptic cation currents (indicated by a dotted arrow ●●●>). **e** a direct (1) or TRPV1-mediated (2) reduction of nNOS activity (indicated by a continue arrow →), ultimately reducing Ca^{2+} concentration in a representative glutamatergic synapse

neurotransmissions, particularly of the metabotropic type, but turns out to be more riveting and challenging since it freely diffuses through aqueous and lipid environments. In fact, with respect to classical neurotransmitters, this feature makes it hard to predict which side of the synapse NO will modulate after being synthesized, suggesting the possibility of simultaneous signals to both pre- and post-synaptic elements, coordinating complex responses (Garthwaite 2008).

In the CNS, nitric oxide participates in synaptic plasticity, axonal elongation and both normal and pathological excitability (Brenman and Bredt 1997; Kiss and Vizi 2001; Sardo and Ferraro 2007; Sardo et al. 2009, 2011). Several studies report that NO acts on neuronal function mainly by regulating neuroexcitability and neurotransmitter release (Ahern et al. 2002; Prast and Philippu 2001), though it still needs to be figured out whether nitrergic-induced changes in neuronal excitability and synaptic strength are exerted on pre- and/or post-synaptic locations, depending on the circuit. One of the main target of NO activity is the redox site of the post-synaptic, glutamatergic NMDA receptor decreasing its response to agonists, especially during ''over-activity'' (Grima et al. 2001; Quesada et al. 1996); but it also participates in metabotropic GLU receptor-dependent LTP (Anwyl 2009). All considered, NO has been implicated in the genesis and the spreading of the epileptiform hyperexcitability (Przegalinski et al. 1996). Several observations have revealed a general increase in NOS expression in various models of experimental epilepsy (Hara et al. 1997; Lumme et al. 2000), though no definitive conclusions have been released about a pro- or anticonvulsant role so far probably due to a complex tuning of neurotransmission systems, above all of glutamate and GABA (Borowicz et al. 2000; de Vasconcelos et al. 2000; Del-Bel et al. 1997; Ferraro and Sardo 2004).

Nitrergic interplay with TRPV1/CB_1R

Within the context of hyperexcitability, a novel interpretation could be suggested considering the implication of post-synaptic NO in CB_1–TRPV1 signalling that has been recently reported in various neuronal processes. NO has caught attention not only since it likely represents a target but also a mediator of cannabinoid action (Bahremand et al. 2009; Jones et al. 2008; Kim et al. 2006a), directly via

CB_1-activated pathway or via post-synaptic TRPV1 (Aguiar et al. 2014; Batista et al. 2015; Bredt and Snyder 1989) (Fig. 3). In particular, cannabinoid agonists can stimulate both the production of cGMP and the translocation of the NO-activated sGC (Jones et al. 2008). Anatomical evidence point to a co-localization of nNOS and NO-activated sGC in synapses supplied with CB_1 receptors, especially in the hippocampus (Azad et al. 2001; Burette et al. 2002; Makara et al. 2007). Furthermore, cannabinoids were reported to inhibit nNOS activity in brain processes, for instance, blocking K^+-induced depolarization (Hillard et al. 1999) and reducing voltage-gated Ca^{2+} influx, therefore, uncoupling membrane depolarization from nNOS activation (Twitchell et al. 1997). In this regard, we have recently shown that in two different models of TLE, the inhibition of nNOS reinforces the antiepileptic effects of WIN (Carletti et al. 2015). Noteworthy, TRPV1 was also found to target post-synaptic nNOS, since systemic administration of CAP increased NO synthesis in the hypothalamus and amygdala in rats, whereas TRPV1 antagonists impaired NO-induced effects (Lisboa et al. 2013; Okere et al. 2000).

A turning point on this controversial issue was recently made by Zschenderlein and his group (2011), among the few providing electrophysiological data correlating CB, TRPV and NO activity in the lateral amygdala. This relevant paper stated that long-term potentiation is dependent on TRPV1, gated by CAP and modulated by cannabinoids, influencing NO-mediated glutamatergic transmission. The reported data support that AEA could modulate NO levels by two plausible pathways. On one hand, AEA could diminish the activity of nNOS via cannabinoid receptors; on the other, it could stimulate NO synthesis via TRPV1. In accordance with this view, behavioural experiments were then performed to correlate the activity of cannabinoids to NO levels via modulation of TRPV1 upon microinjection of AEA, of a TRPV1 antagonist and of NO scavenger in the rat periaqueductal grey (Aguiar et al. 2014; Batista et al. 2015). It was shown that TRPV1 antagonists and NO scavenger determine anxiolytic-like effects that were both reverted by CB_1 antagonist in this brain area, suggesting that aversive response is mediated by CB_1R-facilitated GLU release (Batista et al. 2015).

These fascinating evidence allow to speculate on a possible common intracellular target for CB and TRPV1 signalling, i.e. the nNOS. Henceforth, our lab shed new light on the fact that in the paroxysmal activation of hippocampal dentate gyrus, TRPV1 could affect the nitrergic modulation of the antiepileptic effects exerted by CB agonist, WIN (Carletti et al. 2017). Pharmacological manipulation of this pathway in an electrically induced model of TLE in vivo showed that the blockade or the promotion of the NO production modified oppositely the influence of TRPV1 activation on cannabinoid antiepileptic activity. Indeed, the systemic administration of 7NI attenuated CAP impairment of WIN protective effects, whereas providing L-arginine as a precursor of NO for nNOS, this effect was counteracted. These data obtained influencing NO amounts substantiate the significance of nNOS activity in the control of hippocampal excitability exerted by interaction of CB and TRPV1 receptors (Tahmasebi et al. 2015). In fact, the activity of the enzyme-producing NO appears to be stimulated by TRPV1 and inhibited by cannabinoids (Benko et al. 2005; Kim et al. 2006a, b; Zschenderlein et al. 2011).

In accordance with this idea, the conflicting action of CB and vanilloid systems on paroxysmal phenomena could be ascribed to the antagonism on nNOS function (Aguiar et al. 2014; Batista et al. 2015; Zschenderlein et al. 2011). In this viewpoint, CB, TRPV1 and NO could not only be depicted as three sides of the same triangle, in which cannabinoid and TRPV1 converge on modulating nNOS, but also mutually interact with the ultimate goal of balancing electric currents (Fig. 3). This modulatory mechanism may occur by an independent action of the two receptors converging on the same target or, alternatively, nNOS could represent a link between CB_1 and TRPV1 functions. Nitrergic system might be ideally positioned downstream TRPV1 action, in this way, mediating post-synaptic CB signalling that gate downstream pathways influencing neuronal firing. One possible explanation is provided by the finding of a NO-sensitive gate in TRP family channels. It seems that a rise in the levels of intracellular NO is responsible for TRPV1 activation upon nitrosylation of cysteine residues of the receptor (Nazıroğlu 2015; Yoshida et al. 2006). This linked action between NO and TRP channels could constitute a positive feedback circuit leading, when excessive, to hyperexcitability states. As reported in a model of hippocampal neurotoxicity, the administration of a TRP agonist increased NO amounts following activation of nNOS (Hong et al. 2016). Accordingly, vanilloid and nitrergic systems could constitute a detrimental loop that could favour cell depolarization, ultimately exerting a synergic influence on the proneness of hippocampal neurons to generate burst discharge. The CB action could likely play a fundamental role to maintaining a balanced control of neuronal excitability reducing the effects induced by the interaction of vanilloid and nitrergic systems.

Molecularly, it could be hypothesized that the opposite action of CB and TRPV1 on nNOS could be related to the levels of intracellular Ca^{2+} and glutamate release. In this regard, the on-demand CB synthesis in hyper-excited glutamatergic synapses reduces glutamate release and its triggered pathway (Castillo et al. 2012; Jones et al. 2008; Marsicano et al. 2003; Monory et al. 2006). Over-activation of NMDARs by glutamate typically induces Ca^{2+} influx in the cells and its release from internal organelles, stimulating the Ca^{2+}-calmodulin/adenylyl cyclase/cAMP/PKA pathway. In response to the elevated Ca^{2+} level, nNOS produces NO, triggering apoptotic cascade and neurotoxicity. According

to some authors, cannabinoids can reduce Ca^{2+} elevation by acting directly on the NMDAR rather than by promoting its reuptake or expulsion into the extracellular space (Sensi and Jeng 2004; Zhuang et al. 2005). In particular, CB_1R were found to co-internalize with the subunit NR1 of NMDA in the post-synapse in mouse brain to neutralize excessive expression of NMDA and consequently reduce NO production (Sánchez-Blázquez et al. 2013). Cannabinoids that induce strong internalization of CB_1Rs after agonist challenge such as WIN and ACEA (Garzòn et al. 2009; Hsieh et al. 2002) could be considered better neuroprotectors than those exerting weak internalization like AEA. Indeed, WIN is responsible for a rapid restoration of CB_1Rs on the membrane surface in analgesia, probably by recycling internalized receptors and adding newly synthesized ones, with the ultimate effect of reducing CB_1R desensitization and promoting CB-mediated neuroprotection (Garzòn et al. 2009). In contrast, TRPV1 currents were suggested to elevate intracellular Ca^{2+} levels, to induce NO synthesis and thus to set off the release of glutamate (Szallasi and Blumberg 2007; Xing and Li 2007; Uliana et al. 2016; Zschenderlein et al. 2011). Indeed, TRPV1 can not only directly gate extracellular Ca^{2+} into cells, but are also controlled by G-protein-coupled receptors GPCRs (De Petrocellis and Di Marzo 2009). Data provided by Fawley et al. (2014) suggest that pre-synaptic Ca^{2+} entry via TRPV1 has priority access to the vesicles released to drive spontaneous release also independently from afferent activity or voltage. This direct action on Ca^{2+} entry is also responsible for TRPV1 rapid activation-induced desensitization, because Ca^{2+}-dependent calcineurin dephosphorylates several TRPV1 residues necessary for its activity (De Petrocellis and Di Marzo 2009; Mohapatra and Nau 2005). A specific inhibition was reported by WIN on the TRPV1 function via dephosphorylation processes that desensitizes vanilloid channels in models of nociception (Jeske et al. 2006; Patwardhan et al. 2006), providing further support to complex regulatory mechanisms implying calcium signalling.

To conclude, nNOS emerges as a plausible point of interaction of CB_1 and TRPV1 in the context of glutamatergic transmission. Nevertheless, the reviewed evidence allows to hypothesize that CB and vanilloid systems could be more complexly intertwined, and this deserves to be further investigated.

Final remarks

The current review broadens knowledge on novel CB-mediated interactions in the modulation of hippocampal function within the remit of hyperexcitability phenomena.

Considering the reviewed literature, the implication of nNOS emerges as a common target of cannabinoids and TRPV1 on which their opposite actions converge to regulate calcium-sustained hyperexcitability. The data examined support the speculation that a pathophysiological unbalance of CB_1R/TRPV1 and nitrergic signalling systems could be associated with bioelectrical alterations of synaptic processes, thus influencing experimental epileptic conditions. Therapeutic implications of cannabinoids and related pharmacological tools in refractory, partial complex epilepsy that frequently fail to be controlled are an outstanding value of basic research on the topic. Remarkably, the pharmacological manipulation of CB/TRPV1 pathway through nitrergic signalling could constitute a promising strategy to finely tune cannabinoid therapeutic efficacy, excluding adverse consequences due to their psychoactive toxicity. The development of novel therapeutic agents targeting specific molecular players involved in the anticonvulsant action of cannabinoids may have face validity within the clinical setting.

In this context, our review innovatively answers to several questions that have been posed to deepen understanding of mechanisms involved in CB signalling, fostering the urgency to further explore the pharmacological potential properties of cannabinoids.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

Ethical approval This is a review of the literature with no animal or human study that could require an ethical approval.

Informed consent This is a review with no experiments performed on humans. All authors of the review agree with the content.

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