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CB2 receptor in the CNS: From immune and neuronal modulation to behavior

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Abstract

Despite low levels of cannabinoid receptor type 2 (CB2R) expression in the central nervous system in human and rodents, a growing body of evidence shows CB2R involvement in many processes at the behavioral level, through both immune and neuronal modulations. Recent *in vitro* and *in vivo* evidence have highlighted the complex role of CB2R under physiological and inflammatory conditions. Under neuroinflammatory states, its activation seems to protect the brain and its functions, making it a promising target in a wide range of neurological disorders. Here, we provide a complete and updated overview of CB2R function in the central nervous system of rodents, spanning from modulation of immune function in microglia but also in other cell types, to behavior and neuronal activity, in both physiological and neuroinflammatory contexts.

Keywords : Endocannabinoid system, cannabinoid receptor 2, neuroinflammation, neuronal activity, behavior.

1. Introduction

Although many cannabinoid receptors have been and continue to be described (Cristino et al., 2020), the roles of the cannabinoid receptors type 1 (CB1R) and type 2 (CB2R) within the central nervous system (CNS) are most documented (Galiègue et al., 1995; Iannotti et al., 2016). CB1R is the most prevalent G protein-coupled receptor (GPCR) in the CNS and is expressed extensively by most neuron types. It is often referred to as the central cannabinoid receptor and is the major mediator of the psychoactive effects of *Cannabis sativa* and its derivatives (Mackie, 2005). CB2R was first described as a peripheral receptor involved in

immunomodulatory functions in leukocytes (Buckley et al., 2000). CB2R is a GPCR mainly coupled to G_{i/o} proteins. Its stimulation triggers inhibition of adenylate cyclase activity and activation of the mitogen-activated protein kinase (MAPK), and is followed by β-arrestin recruitment resulting in receptor desensitization (Bouaboula et al., 1999; Kibret et al., 2022). CB2R intracellular pathways have been recently reviewed (Iannotti et al., 2016) and may differ depending on the tissues, cell types and subcellular localization (Howlett and Abood, 2017). The main intracellular pathways regulated by CB2R are summarized in figure 1.

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Nowadays, due to the emergence of higher sensitivity and specificity techniques, CB2R has been detected in the CNS and with its activity modulated using specific agonists and inverse agonists, we have gained a greater understanding of its involvement in cell functions and behavior (Whiting et al., 2022). Since then, CB2R has received increasing interest in neuroscience research, with targeting of CB2Rs demonstrating great therapeutic promise in many rodent models of neurological diseases. Over the past decades, its involvement in the control of microglial activity and behavior has been widely investigated, as recently reviewed (Jordan and Xi, 2019; Komorowska-Müller and Schmöle, 2020). However, this modulation of behavior is perhaps even broader than previously described, with direct or indirect intervention of other cell types involved, including neurons and infiltrating immune cells in pathological contexts. This review aims to provide a detailed and updated overview of CB2R function in the CNS, spanning from the modulation of immune function in microglia and other cell types, to neuronal activity and the resulting behavior, in both physiological and neuroinflammatory contexts. The specific details of experimental designs, such as; the doses of CB2R activators or inhibitors used, the frequency and the time of treatments (i.e., before, and/or during and/or after the brain injury), are provided in tables. This is to aide in comparisons between studies, to find the elements that may explain results sometimes presented as contradictory, and to guide future experimental design.

2. Tools to tackle CB2R functions

CB2R can be activated by endogenous cannabinoids (endocannabinoids, among which the most extensively studied are anandamide and 2-arachidonylglycerol) or exogenous cannabinoids (phytocannabinoids derived from the *Cannabis sativa* plant, such as Δ^9 -tetrahydrocannabinol or THC and cannabidiol or CBD, figure 1) (Peng et al., 2022; Pertwee, 2008; Schurman et al., 2019). These natural molecules are known to mediate a plethora of physiological effects by activating many distinct receptors. The main cannabinoid receptors are CB1R and CB2R, yet cannabinoids have been reported to interact with several other receptors, ranging from other GPCRs to ion channels and nuclear receptors (Howlett, 2002; Starowicz et al., 2007; Zou and Kumar, 2018). As these molecules identified so far are not selective for CB2R (Cristino et al., 2020), studies investigating their effects on the central nervous system have not been reported in this review. The availability of specific synthetic ligands to CB2R (agonists and inverse agonists) and CB2R Knock-Out (KO) mice (Buckley et al., 2000; López et al., 2018; Zhang et al., 2019) has allowed the study of the biological function of CB2R both *in vitro* and *in vivo*. The current state of CB2R ligand development and progress has been recently reviewed in depth (Whiting et al., 2022). In the present review are included studies that have demonstrated functional implication of CB2R using CB2R KO mice or specific ligands. Also are included studies that used non-selective

agonists, the specific effect of which on CB2R was demonstrated when counteracted by specific inverse agonists/antagonists. Table 1 lists the CB2R ligands used in studies included in this review. Among them, JWH-133 is the most commonly used agonist, yet GP1a currently appears to present the lowest K_i and therefore the highest affinity to CB2R (Murineddu et al., 2006). AM630 is by far the most represented ligand among all the inverse agonists listed in this review, even with JTE-907 having the highest affinity to CB2R (Iwamura et al., 2001).

3. Neuro-immunomodulatory properties of CB2R

3.1. *In vitro* evidence of CB2R immunomodulatory functions

CB2R is known for having strong immunomodulatory properties widely demonstrated in peripheral leukocytes. In the CNS, CB2R expression can be induced in microglia under inflammatory conditions (Benito et al., 2003; Grabon et al., 2023; Komorowska-Müller and Schmöle, 2020; Maresz et al., 2005). CB2R activation by specific agonists has been widely studied *in vitro* under inflammatory conditions in brain cells, especially in primary cultured microglia activated by bacterial lipopolysaccharide (LPS).

3.1.1. Effect on microglial reactivity and polarization

Activation of CB2R with different specific agonists was tested under inflammatory conditions on human, mouse and rat microglial cell lines. The results obtained are reported in Supplementary Table 1, having paid particular attention for each study to the time of CB2R ligand application, i.e., before, during, or following the inflammatory challenge. The results of all the reported studies converge in favor of a reduction in both the expression of pro-inflammatory cytokines and of inducible nitric oxide synthase (iNOS), as well as reduced levels of oxidative molecules related to the M1 polarization state, regardless of when the CB2R agonist was applied (Askari and Shafiee-Nick, 2019a; Ehrhart et al., 2005; Facchinetti et al., 2003; Ma et al., 2015; Malek et al., 2015; Ortega-Gutiérrez et al., 2005; Pan et al., 2020; Ramírez et al., 2005; Ramírez et al., 2012; Ribeiro et al., 2013; Romero-Sandoval et al., 2009; Young and Denovan-Wright, 2022). Activation of downstream pro-inflammatory pathways were also restrained by CB2R stimulation (Sheng et al., 2019; Tang et al., 2015). The expression of M2-related proteins, especially interleukin (IL)-10, arginase (Arg)-1 and cluster of differentiation (CD)206, as well as anti-inflammatory cytokines were found to be increased following CB2R specific activation (Askari and Shafiee-Nick, 2019a; Correa et al., 2010; Ma et al., 2015; Malek et al., 2015). Furthermore, microglia from CB2R deficient mice are not able to polarize toward the anti-inflammatory and cytoprotective M2 phenotype, as they showed a reduced expression of Arg-1 after stimulation with IL-4/IL-13 (Mecha et al., 2015).

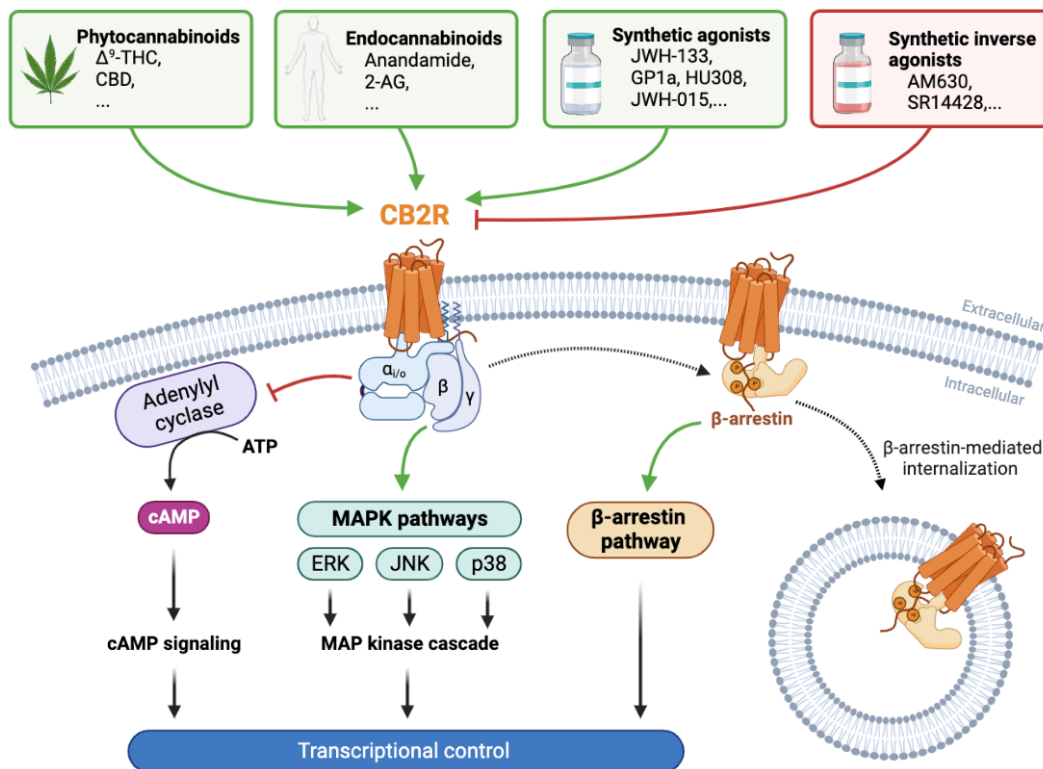


Figure 1. CB2R cellular signaling. The different types of CB2R ligands are represented: phytocannabinoids, endocannabinoids, and synthetic ligands. The major intracellular pathways modulated by the G-protein coupled receptor CB2R are shown in the lower part of the figure. It should be noted that the pathways activated may depend on cell types, ligands and physiological conditions. Figure created with [BioRender.com](https://www.biorender.com). **Abbreviations:** Δ⁹-THC, Δ⁹-tetrahydrocannabinol; 2-AG, 2-arachidonyl-glycerol; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CBD, cannabidiol; ERK, Extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases.

Taken together, these results suggest that CB2R activation plays a major role in resolving microglia-driven inflammation, promoting a switch from M1 to M2 polarization state, even if the distinction between these two states is now considered as caricatural and should be used cautiously (Paolicelli et al., 2022; Ransohoff, 2016).

Some studies have shown intriguing results comparing the effects of CB2R agonists and inverse agonists. In particular, it was shown that CD206 expression was decreased after CB2R activation, whereas it was increased by the specific inverse agonists SMM-189 and SR14428 (Presley et al., 2015). In addition, conflicting conclusions can be drawn when comparing studies that use different CB2R inverse agonists on different cell types and in response to distinct inflammatory challenges. For instance, inverse agonist applied before LPS induced either an increased expression of IL-1β, IL-18 and Tumor Necrosis Factor (TNF)-α with AM630 (Malek et al., 2015), or conversely a reduced release of IL-1β and prostaglandin E2 when using SMM-189 (Yu et al., 2020).

All the data collected so far highlights the full potential of CB2R modulation to resolve inflammation and alter microglial cell function, although our understanding of the mechanisms underlying this modulation remains largely limited due to their complexity.

3.1.2. Effect on other cell types

Production and secretion of cytokines, by monocytes, astrocytes, oligodendrocytes and endothelial cells, following inflammatory challenge were counteracted when stimulated by CB2R agonists (Askari and Shafiee-Nick, 2019b; Correa et al., 2005; Jia et al., 2020; Klegeris et al., 2003; Montecucco et al., 2008; Persidsky et al., 2015; Sheng et al., 2005). In addition, their release of chemokines, involved in the chemoattraction of immune cells toward the inflammatory site, was decreased following CB2R activation (Jia et al., 2020; Persidsky et al., 2015; Sheng et al., 2005) (Supplementary Table 1). Transwell migration assays demonstrated that migration of neutrophils (Murikinati et al., 2010; Porter et al., 2019) and macrophages (Montecucco et al., 2008; Persidsky et al., 2015; Rom et al., 2013) was inhibited when using specific CB2R agonists. Furthermore, a reduction in monocyte/endothelium interaction was demonstrated after CB2R activation in human primary brain microvascular endothelial cells challenged with TNF-α (Rom et al., 2013), concurrent with a decrease in adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 expression (Persidsky et al., 2015; Ramirez et al., 2012). Hence, CB2R can exert its immunomodulatory role by decreasing the recruitment of peripheral leukocytes into inflamed neuronal tissue through limiting both leukocyte chemotaxis and extravasation.

Table 1. CB2R Ligands. Every CB2R ligands used in studies included in this review are listed in this table. Note that AM630, JTE-907, SMM-189, SR144528 have been first described as inverse agonists, as mentioned here, but have also been mentioned as antagonists in many studies. In the "frequency of use" column is presented the number of times each ligand was used among all included studies (studies having used one or more agonists to activate CB2R: n=155; studies having used one or more inverse agonists to study their own effect or to block the effect of an agonist: n=100)

LIGAND	ACTION	IUPAC Nomenclature	Ki (nM)	CB2R/CB1R affinity	Frequency of use	REF
AM1241	CB2R Agonist	(2-Iodo-5-nitrophenyl)-[1-[(1-methylpiperidin-2-yl)methyl]indol-3-yl]methanone	3.4	82:1	12/155	(Ibrahim et al., 2003)
β -caryophyllene	CB2R Agonist	(1R,4E,9S)-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene	155	No affinity for CB1R	14/155	(Gertsch et al., 2008)
CB65	CB2R Agonist	N-Cyclohexyl-7-chloro-1-[2-(4-morpholinyl)ethyl]quinolin-4(1H)-one-3-carboxamide	3.3	303:1	1/155	(Manera et al., 2006)
GP1a	CB2R Agonist	N-(Piperidin-1-yl)-1-(2,4-dichlorophenyl)-1,4-dihydro-6-methylindeno[1,2-c]pyrazole-3-carboxamide	0.037	>9000:1	10/155	(Murineddu et al., 2006)
GW833972A	CB2R Agonist	2-[[3-chlorophenylamino]-N-(4-pyridinylmethyl)-4-(trifluoromethyl)-5-Pyrimidinecarboxamide hydrochloride	7.8	1000:1	2/155	(Belvisi et al., 2008)
GW405833	CB2R Agonist	1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-[2-(4-morpholinyl)ethyl]-1H-indole	3.92	1217:1	4/155	(Gallant et al., 1996)
HU210	CB2R/CB1R Agonist	(6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6H,6aH,7H,10H,10aH-benzo[c]isochromen-1-ol	0.52	1:10	3/155	(Felder et al., 1995)
HU308	CB2R Agonist	[(1R,2R,5R)-2-[2,6-Dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methanol	22.7	No affinity for CB1R	21/155	(Hanus et al., 1999)
HU910	CB2R Agonist	((1S,4R)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol	6	228:1	4/155	(Horváth et al., 2012)
HU914	CB2R Agonist	(1S,4R)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1] hept-2-ene-1-carboxylic acid	1500	No affinity for CB1R	1/155	(Magid et al., 2019)
JWH-015	CB2R Agonist	(2-Methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone	13.8	28:1	18/155	(Showalter et al., 1996)
JWH-133	CB2R Agonist	(6aR,10aR)-3-(1,1-dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6Hdibenzo[b,d]pyran	3.4	200:1	63/155	(Huffman et al., 1999)
MDA7	CB2R Agonist	1-[[3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl]carbonyl]piperidine	238	10:1	4/155	(Naguib et al., 2008)
O-1966	CB2R/CB1R Agonist	1-[4-(1,1-dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3-methyl-cyclohexanol	23.0	220:1	9/155	(Wiley et al., 2002)
O-3853	CB2R Agonist	-	17.3	47:1	1/155	(Zhang et al., 2007)
Paeoniflorin	CB2R Agonist	[(1R,2S,3R,5R,6R,8S)-6-hydroxy-8-methyl-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-9,10-dioxatetracyclo[4.3.1.0 _{2,5} .0 _{3,8}]decan-2-yl]methyl benzoate	-	-	1/155	(Luo et al., 2018a)
RO6871304	CB2R Agonist	(3S)-1-{5-tert-butyl3-[(1-cyclopropyl1H-tetrazol-5-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-ol	34	588:1	1/155	(Porter et al., 2019)
RO6871085	CB2R Agonist	5-Cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-4-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide	6	44:1	1/155	(Porter et al., 2019)
UCM707	Inhibitor of anandamide uptake	(5Z,8Z,11Z,14Z)-N-(3-furylmethyl)eicosa-5,8,11,14-tetraenamide	-	-	1/155	(de Lago et al., 2002)
WIN55,212-2	CB2R/CB1R Agonist	(11R)-2-Methyl-11-[[morpholin-4-yl)methyl]-3-(naphthalene-1-carbonyl)-9-oxa-1-azatricyclo[6.3.1.0 ^{4,12}]dodeca-2,4(12),5,7-tetraene	3.3	1:2	11/155	(Felder et al., 1995)
1-phenylisatin	CB2R Agonist	1-phenylindole-2,3-dione	-	-	2/155	(Jayant et al., 2016)
AM630	CB2R Inverse agonist	1-[2-(Morpholin-4-yl)ethyl]-2-methyl-3-(4-methoxybenzoyl)-6-iodoindole	31.2	165:1	67/100	(Ross et al., 1999)
JTE-907	CB2R Inverse agonist	N-(1,3-benzodioxol-5-ylmethyl)-1,2-dihydro-7-methoxy-2-oxo-8-(pentyloxy)-3-Quinolinecarboxamide	0.38	2760:1	3/100	(Iwamura et al., 2001)
SMM-189	CB2R Inverse agonist	30,50-dichloro-2,6-dihydroxy-biphenyl-4-yl)-phenyl-methanone	1.66	602:1	3/100	(Bhattacharjee et al., 2009)
SR144528	CB2R Inverse agonist	5-(4-Chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-N-[(1S,2S,4R)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrazole-3-carboxamide	0.6	700:1	32/100	(Rinaldi-Carmona et al., 1998)

Abbreviations: CB1R and CB2R, cannabinoid receptor type 1 and 2; IUPAC, International Union of Pure and Applied Chemistry; Ki, dissociation constant; Ref, reference first describing the compound.

3.2. Immunomodulatory properties of CB2R in rodent models of neuroinflammation

CB2R is upregulated in brain inflammatory tissue under different pathological contexts (Benito et al., 2008; Cabral et al., 2008; Grabon et al., 2023; Jordan and Xi, 2019). Numerous studies have provided evidence that CB2R is involved in the modulation of neuroinflammation, when triggered in various

animal models of diverse neurological disorders. Here multiple inflammatory hallmarks have been studied, namely the release of inflammatory cytokines, gliosis, cell polarization and the recruitment of peripheral leukocytes into the brain (Figure 2, Supplementary Table 2).

3.2.1. Inflammatory cytokine expression

The expression of pro-inflammatory cytokines in the neural tissue is one of the main features of neuroinflammation. Pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and Interferon (IFN)- γ are strongly induced in many inflammatory-associated diseases or conditions affecting the nervous system, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), stroke, neuropathic pain, traumatic brain

injury (TBI), spinal cord injury, encephalitis, epilepsy, etc. In line with results obtained from *in vitro* investigations, the specific activation of CB2R was shown to significantly decrease the induction of pro-inflammatory cytokines in inflamed tissue in rodent models (Supplementary Table 2). In some studies using agonists with high CB2R affinity and selectivity, CB2R involvement has been ensured by the loss of effect with the use of inverse agonists (Chung et al., 2016; Javed et al., 2016; Li et al., 2018; Tang et al., 2015; Tao et al., 2016; Toguri et al., 2014; Torres et al., 2010; Viveros-Paredes et al., 2017a; Youssef et al., 2019) or by the lack of the expected effect in transgenic mice that do not express CB2R (CB2R KO) (Gómez-Gálvez et al., 2016; Porter et al., 2019).

This modulatory effect was observed in preventive strategies, when agonists were administered before induction of the disease or the injury, namely in rodent models of HD (Sagredo et al., 2009), LPS-induced inflammation (Sahu et al., 2019a), 3,4-methylenedioxy-N-methylamphetamine (MDMA)-induced inflammation (Torres et al., 2010), neonatal stroke (Tang et al., 2016), seizures (Karan et al., 2021) and PD (Chung et al., 2016; Javed et al., 2016).

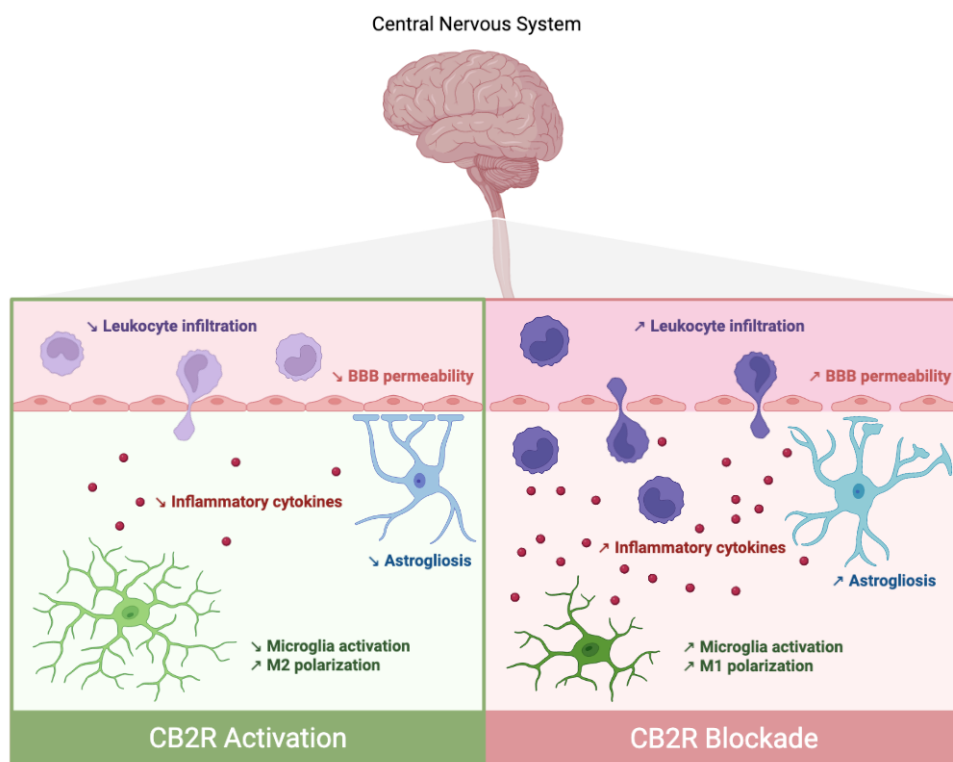


Figure 2. Summary of immunomodulatory effects of CB2R in the central nervous system. This figure depicts the main outcomes on neuroinflammation following CB2R modulation described in section 3. The main effects of pharmacological activation of CB2R by treatment with specific agonists are summarized on the left side of the figure. The majority of the studies included in this review converge in favor of an anti-inflammatory effect of CB2R activation, with a reduction in the: 1) activation of both microglia and astrocytes, 2) expression of cytokines and other inflammatory molecules, 3) permeability of the blood-brain barrier (BBB), and 4) infiltration of leukocytes (neutrophils, T lymphocytes, monocytes depending on the context). The effects of blocking CB2R activity (genetically using KO mice or pharmacologically with specific antagonists) are shown on the right side of the figure. Blockade of CB2R mostly leads to pro-inflammatory effects, with exacerbation of microglia and astrocyte activation, inflammatory molecules expression, BBB permeability and peripheral immune cell infiltration. Figure created with BioRender.com

When administered after triggering of the pathological condition in animal models, CB2R agonists attenuated overexpression of pro-inflammatory molecules, as shown in models of AD (Çakır et al., 2019; Fakhfouri et al., 2012; Wu et al., 2013), MS (Croxford and Miller, 2003; Kong et al., 2014a), uveitis (Toguri et al., 2014), vascular dementia (Luo et al., 2018a), stroke (Tang et al., 2015; Tao et al., 2016; Zarruk et al., 2012), sepsis (Çakır et al., 2020; Yang et al., 2022), intracerebral hemorrhage (Li et al., 2018; Lin et al., 2017), human immunodeficiency virus (HIV)-1 encephalitis (Gorantla et al., 2010), PD (Rentsch et al., 2020), TBI (Amenta et al., 2014; Braun et al., 2018; Magid et al., 2019), spinal cord injury (Adhikary et al., 2011), surgery-induced neuroinflammation (Sun et al., 2017), sub-chronic stress-induced inflammation (Zoppi et al., 2014), high fat diet (Youssef et al., 2019) and hypertension-induced neuroinflammation (Shi et al., 2020). Interestingly, peripheral treatment with inverse agonist SMM-189 was also shown to decrease the expression of pro-inflammatory cytokines induced by status epilepticus in mice (Yu et al., 2020), suggesting that both agonists and inverse-agonist may exert anti-inflammatory properties under certain conditions. Chronic administration of CB2R agonists in AD models after the onset on the neuroinflammatory state also resulted in a decrease in the expression of pro-inflammatory mediators (Aso et al., 2013; Martín-Moreno et al., 2012). In certain cases, the decrease in pro-inflammatory cytokines following CB2R activation was accompanied by an increase in the expression of anti-inflammatory cytokines, as observed in models of stroke (Tao et al., 2016), spinal cord injury (Adhikary et al., 2011) or TBI (Braun et al., 2018).

CB2R activation by agonists in the vast majority of cases, and sometimes by inverse agonists, can therefore exert powerful preventive and curative effects on the induction of pro-inflammatory cytokines.

However, as for the *in vitro* studies, the effects of CB2R inverse agonists used alone on inflammatory cytokine induction are more contrasted. Cytokine induction remained unchanged in a model of stroke (Tang et al., 2016), was upregulated in surgery-induced neuroinflammation (Sun et al., 2017), downregulated in a model of uveitis (Toguri et al., 2014) and inconsistent in TBI, being either unchanged (Braun et al., 2018) or upregulated (Amenta et al., 2014). These intriguing effects may be explained by the variety of the doses, time and modes of administration of the drugs, and by the time measurements were made.

3.2.2. Gliosis

3.2.2.1. Microglia

Pre-treatment with CB2R agonists showed a significant reduction of microglial activation in inflamed tissue of animal models of chronic post-ischemia pain (Xu et al., 2016), MDMA-induced neuroinflammation (Torres et al., 2010), neonatal stroke (Tang et al., 2016), paclitaxel-induced neuro-

inflammation (Wu et al., 2019), Theiler's virus induced demyelination disease (Mecha et al., 2018), CO-induced cognitive deficit (Du et al., 2020), hemicerebellectomy (Oddi et al., 2012) and PD (Chung et al., 2016; Javed et al., 2016; Viveros-Paredes et al., 2017a). Activation of CB2R during or after induction also lead to a decrease in microgliosis in rodent models of high-fat diet induced-neuroinflammation (Rorato et al., 2022), morphine-hyperalgesia (Tumati et al., 2012), AD (Wu et al., 2013), HIV1-encephalitis (Gorantla et al., 2010), intracerebral hemorrhage (Li et al., 2018), MS (Alberti et al., 2017; Kong et al., 2014b, 2014a; Ortega-Gutiérrez et al., 2005), PD (Gómez-Gálvez et al., 2016; Rentsch et al., 2020), spinal cord injury (Adhikary et al., 2011), neuropathic pain (Klauke et al., 2014), stroke (Tang et al., 2015; Tao et al., 2016; Yu et al., 2015; Zarruk et al., 2012), surgery-induced neuroinflammation (Sun et al., 2017), TBI (Elliott et al., 2011), vascular dementia (Luo et al., 2018a) and retinal inflammation (Spyridakos et al., 2021). Finally, chronic activation of CB2R in AD (Aso et al., 2013; Li et al., 2019a; Martín-Moreno et al., 2012; Wu et al., 2017) and in amyotrophic lateral sclerosis (ALS) (Espejo-Porras et al., 2019) mouse also resulted in a decrease in microglial activation. Microglial cells sensitivity to CB2R activation under inflammatory state is consistent with *in vitro* observations and with the fact that CB2R expression was shown to be induced in this cell population in such conditions (Grabon et al., 2023; Komorowska-Müller and Schmöle, 2020).

Given that microglia are considered as one of the major contributors of inflammatory cytokine secretion under pathological conditions, the limitation of microglial activation may be at least one explanatory factor of the decrease in pro-inflammatory cytokine induction observed following CB2R activation.

3.2.2.2. Astrocytes

In most studies reporting the effect of CB2R activation on astrogliosis, glial fibrillary acid protein (GFAP) expression was found to be either unchanged, as in a HIV-encephalitis (Gorantla et al., 2010) and AD (Martín-Moreno et al., 2012) models (Supplementary Table 2) or downregulated in ALS (Espejo-Porras et al., 2019), PD (Chung et al., 2016; Javed et al., 2016; Rentsch et al., 2020; Viveros-Paredes et al., 2017a), spinal cord ischemia (Jing et al., 2020), neuropathic pain (Klauke et al., 2014), morphine-mediated inflammation (Tumati et al., 2012), and in a different AD model (Wu et al., 2013). Unexpectedly, astrogliosis was found to be exacerbated following CB2R agonist administration and reduced with an inverse agonist in another AD mouse model (Esposito et al., 2007). CB2R activation appears to have potent opposite effects on astrogliosis depending on the animal model used, on the time-window of treatment and on the time of data collection, due to astrogliosis being a dynamic process and to CB2R having complex immunomodulatory properties. CB2R expression has been poorly investigated in astrocytes. It was detected in GFAP-positive cells in the

substantia nigra of PD patients (Navarrete et al., 2018) and in the striatum in a HD rat model (Sagredo et al., 2009), but the specificity of the antibodies used in these studies has not been validated. *In vitro*, CB2R mRNA was detected at low level in enriched primary cultured astrocytes (Carlisle et al., 2002). Nevertheless, CB2R activation may also have indirect effects on astrocytes through microglia for example.

3.2.3. Leukocyte brain invasion

3.2.3.1. Peripheral leukocyte detection in the CNS

The number of infiltrating immune cells in inflamed neural tissue was found to be downregulated by both pre- and post-treatment with CB2R agonist. Namely, T-cells, macrophages and/or neutrophils were found to be fewer in rodent models of PD within the substantia nigra (Chung et al., 2016) and the striatum (Gómez-Gálvez et al., 2016), neuropathic pain within the spinal cord (Sheng et al., 2019), MS within the spinal cord (Kong et al., 2014b, 2014a), stroke within the ischemic cortex (Yu et al., 2015), TBI within the cortex (Braun et al., 2018), in injured spinal cord (although not significant) (Adhikary et al., 2011), and uveitis in eyes (Toguri et al., 2018).

3.2.3.2. Chemotaxis (chemokine expression)

The induction of chemokines was shown to be decreased by CB2R activation in rodent models of PD, MS, spinal cord injury, stroke, surgery-induced neuroinflammation, TBI and uveitis (Supplementary Table 2). However, treatment with AM630, a CB2R inverse agonist, resulted in more contrasted outcomes as chemokine expression was either increased following a surgery-induced cognitive impairment model (Sun et al., 2017), unchanged in a TBI model (Braun et al., 2018) or decreased in an uveitis model (Toguri et al., 2014).

3.2.3.3. Blood brain barrier (BBB) permeability

The migration of peripheral leukocytes into the CNS is made possible under neuroinflammatory conditions by the BBB leakage due to the induction of metalloproteases such as MM9 and the decrease in tight junction protein expression, such as zonula-occludens-1 or claudin-5. This permeability can be measured with different methodological approaches, namely via tracing labeled-proteins normally unable to cross the BBB under physiological conditions. The BBB permeability induced by neuroinflammatory conditions was found to be decreased by CB2R activation in rodent models of PD (Chung et al., 2016), spinal cord ischemia (Jing et al., 2020), LPS-induced inflammation (Ramirez et al., 2012), intracerebral hemorrhage (Li et al., 2018), and TBI (Supplementary Table 2).

3.2.3.4. Leukocyte vessel adhesion

Following CB2R activation in cultured endothelial cells from human brain, there is a reduced expression of specific adhesion molecules (VCAM, ICAM), that play an essential role in the interaction between leukocytes and endothelial cells,

together with a reduced BBB permeability (Ramirez et al., 2012). Vessel adhesion of leukocytes has also been assessed *in vivo* following CB2R activation by intravital fluorescence microscopy and revealed reduced leukocyte/endothelium interactions in a focal ischemia/reperfusion model (Supplementary Table 2).

Overall, these results argue that CB2R can modulate neuroinflammation by controlling peripheral leukocytes invasion in the nervous tissue.

3.2.4. Cell polarization

In agreement with the *in vitro* data, *in vivo* results obtained in rodent models of AD (Li et al., 2019a), intracerebral hemorrhage (Lin et al., 2017), TBI (Li et al., 2022), vascular dementia (Luo et al., 2018a) and stroke (Tao et al., 2016) show that CB2R activation promoted the change of microglial cell polarization from the proinflammatory M1 to the anti-inflammatory M2 phenotype. In a study that distinguished macrophages from microglial cells, CB2R activation caused cortex-infiltrating macrophages to display M2 phenotypic features in a TBI mouse model (Braun et al., 2018).

Hence, CB2R may act as a regulator of neuroinflammation not only by modulating activation of resident glial cells but also by controlling the number of peripheral leukocytes migrating to the CNS and their inflammatory state (Figure 2).

3.3. Insight from CB2R KO mice

CB2R's immunomodulatory role was demonstrated in models of MS, TBI and subchronic stress-induced neuroinflammation, that its deletion resulted in an increase in pro-inflammatory cytokine expression compared with wild-type (WT) littermates (Supplementary Table 3). Production of iNOS was also 10-fold higher in CB2R KO mice subjected to TBI (Amenta et al., 2014). Gliosis was exacerbated in hypoxia-ischemia (Kossatz et al., 2016), ALS (Rodríguez-Cueto et al., 2021), age-related cognitive-decline (Komorowska-Müller et al., 2021a), isoflurane-induced inflammation (Li et al., 2021), neuropathic pain (Racz et al., 2008), α -synuclein fibril-induced inflammation (Feng et al., 2022), MS (Shao et al., 2014) and PD (Gómez-Gálvez et al., 2016) models established in CB2R KO mice. Conversely, gliosis was reduced in a model of LPS and IFN- γ -induced inflammation (Reusch et al., 2022). BBB permeability was found to be enhanced in a TBI model (Amenta et al., 2014), alongside elevated endothelium/leukocyte interactions (Porter et al., 2019; Toguri et al., 2018). Adhesion of leukocytes to endothelium was not increased in LPS-induced neuroinflammation in CB2R KO mouse, though the complete resolution of inflammation took longer (Ramirez et al., 2012). Inconsistent results were obtained from genetic models of AD established in different CB2R KO mouse strains. Here, an exacerbation of the inflammatory state could have been expected as in other inflammatory models. In fact, CB2R deletion either resulted in unchanged IL-1 β expression and microglial activation (Koppel et al., 2014; López et al., 2018) or it resulted in a

decrease in gliosis (Ruiz de Martín Esteban et al., 2022; Schmöle et al., 2018), pro-inflammatory cytokine and chemokine expression and macrophage infiltration (Schmöle et al., 2015) depending on AD mouse model used. These conflicting data may be due to the genetic etiology of the various AD models and the use of different CB2R KO mouse strains.

4. Neuronal activity modulation by CB2R

CB1R is highly expressed in the CNS at the neuronal level and functionally modulates presynaptic neurotransmitter release (Araque et al., 2017; Howlett, 1998). In stark contrast to the vast amount of literature on CB1R-mediated neuromodulation, very little is known about the relevance of CB2R in neuronal signaling. While the neuronal expression of CB2R has been a matter of debate over the past decade, accumulating evidence supports that CB2R plays a role in neuronal activity modulation. Here, we report evidence emerging from both *in vitro* (Supplementary Table 4) and *in vivo* (Supplementary Table 5) supporting CB2R involvement in the modulation of neuronal activity in various brain regions and neuronal subtypes (Figure 3).

4.1. Neurotransmitter release

The impact of CB2R on both excitatory and inhibitory neurotransmitter release has been studied *in vitro*. Bath application of specific agonists resulted in a reduction of evoked gamma-aminobutyric acid (GABA) release (Andó et al., 2012), capsaicin induced calcitonin gene-related peptide (CGRP) release (Beltramo et al., 2006) and K⁺-stimulated Glutamate (Sánchez-Zavaleta et al., 2018) and dopamine release (López-Ramírez et al., 2020) (Supplementary Table 4). Microdialysis studies have revealed additional insights into the effects of CB2R signaling on neurotransmitter release *in vivo*. The effect of CB2R specific activation has been particularly investigated on dopamine release in the nucleus accumbens of rodents. Under physiological conditions, CB2R local activation resulted in a significant drop in extracellular dopamine in a dose-dependent manner. This effect was blocked by an inverse agonist administration and was absent in CB2R KO mice (Xi et al., 2011). Likewise, CB2R pharmacological activation dose-dependently reduced the cocaine- and morphine-mediated rises of extracellular levels of dopamine (Grenald et al., 2017; Xi et al., 2011). However, the extracellular dopamine level in the nucleus accumbens of healthy rats remained unchanged when challenged with the same agonist in a different study, likely because of the systemic route of administration (Zhang et al., 2017). In a rodent model of PD, CB2R activation led to an increase in dopamine and serotonin levels in the striatum (Shi et al., 2017). In the hippocampus, local infusion of JWH-133 reduced ischemia-enhanced extracellular glutamate (Zheng et al., 2015). Taken together, these studies provide further evidence that CB2R activation acts in multiple brain regions to modulate neurotransmitter release.

4.2. Ionic currents

Several lines of electrophysiological evidence indicate that activation of CB2R can modify neuronal activity through ionic current modulation. *In vitro*, JWH-133 bath application on medial prefrontal cortex (mPFC) slices dose-dependently evoked Cl⁻ currents as measured by whole-cell current and voltage clamp recordings (den Boon et al., 2014) and increased intracellular calcium levels (den Boon et al., 2012). T-type Ca²⁺ current amplitude was shown to be increased by CB2R activation in isolated retinal ganglion cells (Qian et al., 2017), as well as M-type K⁺ current amplitude in dopaminergic neurons of VTA slices (Ma et al., 2019). These effects were both prevented by AM630 application (Supplementary Table 4). *In vivo*, calcium imaging revealed that local JWH-133 administration in the spinal cord attenuated capsaicin evoked intracellular calcium increase in a spinal nerve ligation rat model (Sagar et al., 2005).

4.3. Membrane potential

Neuronal membrane potential was shown to be differentially shifted by CB2R activation in a cell type-specific and a region-specific manner. CB2R agonist bath application resulted in a transient delayed depolarization in layer II/III pyramidal neurons of rat mPFC slices and had no effect in CB2R KO mice (den Boon et al., 2012), whereas CB2R specific activation hyperpolarized dopaminergic neurons isolated from mouse VTA (Zhang et al., 2017, 2014). HU-308 was also shown to induce a hyperpolarization in CA3 pyramidal cells of mouse hippocampus *in vivo*. This effect of CB2R activation was directly mediated by neurons as the membrane potential remained unchanged in mice with conditional KO of CB2R in synapsin-positive neurons (Syn-CB2R cKO mice) (Stempel et al., 2016), providing evidence that functional CB2Rs are indeed expressed by neurons in the hippocampus.

4.4. Neuronal excitability

Further *in vitro* and *in vivo* electrophysiological studies brought insights on CB2R involvement in neuronal excitability, namely by assessing neuronal spontaneous or evoked action potentials (AP) firing rate and duration, or by measuring the afterhyperpolarization (AHP). Bath application of CB2R specific agonists on mPFC, VTA, midbrain or substantia nigra pars compacta (SNc) slices resulted in a decreased excitability (den Boon et al., 2012; Ma et al., 2019; Yu et al., 2021; Zhang et al., 2021, 2017, 2014) of pyramidal and dopaminergic neurons, respectively. Conversely, inverse agonist application raised pyramidal neurons excitability in mPFC slices. Neither the agonist nor the inverse agonist had any effect on the excitability of neurons from CB2R KO mice (den Boon et al., 2012). *In vivo*, neuronal excitability was also shown to be decreased by CB2R activation in thalamic ventral posterior nucleus neurons (Jhaveri et al., 2008), in spinal wide dynamic range neurons (Elmes et al., 2004; Nackley et al., 2004), in dorsal horn neurons (Sokal et al., 2003), in CA3

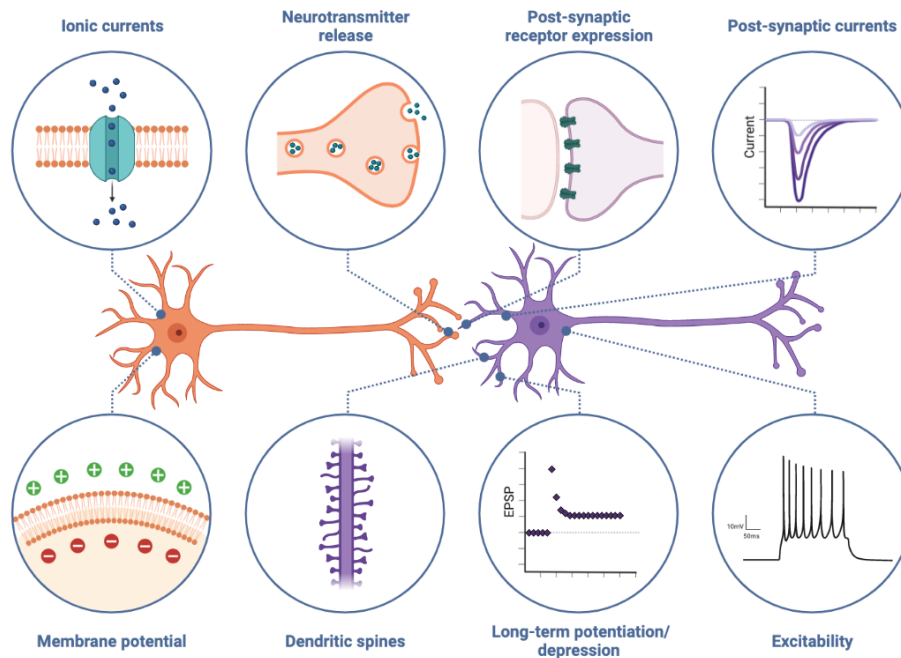


Figure 3. Neuronal activity outcomes following CB2R activation or blockade. This figure summarizes the main mechanisms involved in the modulation of neuronal activity that can be modulated following CB2R activation or blockade, as described in section 4. It should be noted that these modulations were each demonstrated in specific neuronal subpopulations (supplementary table 4 and 5). Figure created with BioRender.com

pyramidal cells (Stempel et al., 2016) and in VTA dopaminergic neurons (Zhang et al., 2014).

4.5. Synaptic transmission

The effect of CB2R activation has also been studied at the synaptic level *in vitro* by monitoring spontaneous, miniature, or evoked post-synaptic currents (PSC). In the hippocampus, activation of CB2R by specific agonists resulted in a higher miniature excitatory PSC (mEPSC) frequency without impacting their amplitude nor inhibitory currents. CB2R-mediated hyperpolarization observed in CA3 did not result from an alteration of evoked IPSC amplitude or field excitatory post-synaptic potential, suggesting that it would be a solely self-regulatory cell-intrinsic mechanism (Stempel et al., 2016). CB2R activation in hippocampus slices also resulted in higher field EPSC (Hwang et al., 2020). In entorhinal cortex and cerebellum slices, amplitude of spontaneous inhibitory PSC recorded in Layer II-V neurons (Morgan et al., 2009) and Purkinje cells (Sadanandan et al., 2020) was reduced by CB2R agonist application, further suggesting that neuronal activity can be modulated by CB2R at the synaptic level. In addition, when CB2R was transfected into CB1R null neurons, depolarization suppression of excitation (DSE) was restored (Atwood et al., 2012). DSE, known to be mediated by CB1R, is the result of a post-synaptic endocannabinoid production that leads to presynaptic inhibition at excitatory synapses and is a form of short-term synaptic plasticity that shortly suppresses neurotransmission (Kano et al., 2009). Restoration of DSE following CB2R transfection into CB1R null neurons further highlights CB2R potency for synaptic transmission modulation. Synaptic transmission can also be indirectly modulated by regulation

of neurotransmitter receptor expression, as it was shown for 5-HT_{2A} receptor in a neuronal cell culture following CB2R specific activation (Franklin and Carrasco, 2012).

4.6. Synaptic plasticity

CB2R can also modulate neuronal function through synaptic plasticity mechanisms. Namely, in mouse hippocampal slices, HU-308 bath application was shown to mimic AP-Driven long-lasting hyperpolarization i.e. slow self-inhibition in CA3 pyramidal neurons. This effect was absent in CB2R KO mice and in Syn-CB2R cKO mice, demonstrating a cell-intrinsic mechanism specifically induced by neuronal CB2R (Stempel et al., 2016). The same phenomenon was observed in Layer II/III regular spiking non-pyramidal cells (RNSCP) interneurons recorded in somatosensory cortical slices and was prevented by inverse agonist application. As for the previous study, the agonist did not have any effect on cortical slices from KO animals (Stumpf et al., 2018). *In vivo*, chronic treatment with specific CB2R agonist MDA-7 in AD mice protected long term potentiation (LTP) in CA1 neurons (Wu et al., 2017, 2013).

CB2R's role in sustaining LTP has been further confirmed in a study which showed that LTP was reduced in CB2R KO mice (Li and Kim, 2016a).

4.7. Dendritic spines

Spine density modulation is a potent cellular mechanism underlying synaptic function. Spine density of CA1 pyramidal cells was enhanced after chronic CB2R activation using JWH-133 or GP1a in organotypic hippocampal slices (Kim and Li,

2015). In addition, CB2R has been shown to be involved in the protection of dendritic spine dynamics, which is impaired after isoflurane exposure, and exacerbated in the hippocampus of CB2R KO mice compared to WT mice (Li et al., 2021).

Overall, evidence shows that CB2R displays region- and cell type-specific modulation of neuronal activity by acting on both the intrinsic excitability and synaptic events at the network level. So far, direct evidence for the neuronal expression of CB2R is still sparse, due to the lack of specific antibodies and neuron-specific genetic manipulations. It is therefore challenging to hypothesize on the potential mode of action of CB2R on the modulation of neuronal activity at the synaptic level. The expression of CB2R in other cell types, including microglia, is more consensual. Since microglia is known to modulate neuronal transmission (Marinelli et al., 2019; Salter and Beggs, 2014), invalidating CB2R gene expression in specific neuronal populations may contribute to elucidate the role of neuronal CB2Rs on neuronal transmission, as already performed in CA3 hippocampal neurons (Stempel et al., 2016).

5. Behavior modulation by CB2R

Aside from its immunomodulatory role, CB2R is now widely known to influence behavior. The effects of CB2R modulation on behavior in neuroinflammatory contexts can be explained by the modulation that CB2R exerts directly on inflammation (see section 3). However, the fact that CB2R also exerts effects on behavior in physiological contexts implies that CB2R dependent mechanisms other than neuroinflammation may govern behavior. Here, we report studies that have provided evidence for the involvement of CB2R in different functions, under physiological and pathophysiological conditions: feeding, motor function, learning and memory, mood regulation, reward, analgesia and seizure.

5.1. Feeding

CB2R pharmacological activation led to different outcomes on feeding behavior depending on studies (Supplementary Table 6). Food intake was either unchanged (Martín-Sánchez et al., 2019) or reduced (Verty et al., 2015) following one single administration of a CB2R specific agonist. In diet-induced obesity models, chronic CB2R activation reduced food intake during the first six days and the body weight along the entire treatment duration, while decreasing feed efficiency ratio (Verty et al., 2015), and diminishing the visceral fat index (Youssef et al., 2019). In a PD model, treatment with a CB2R agonist prevented weight loss (Shi et al., 2017). In mice overexpressing CB2R, basal food intake remained unchanged but fasting-induced intake was reduced (Romero-Zerbo et al., 2012). Inversely, CB2R KO mouse food intake and visceral fat mass are greater than in WT mice (Agudo et al., 2010; Schmitz et al., 2016). The use of inverse agonists brought more contrasted results. Here, AM630 administration led to either unchanged (Martín-Sánchez et al., 2019) or lower (Adamczyk

et al., 2012; Ishiguro et al., 2010) food intake in rodents, or also a higher food intake after 12h food deprivation (Ishiguro et al., 2010). Of the 9 studies that provided evidence of CB2R-mediated modulation of feeding behavior, one showed a concomitant anti-inflammatory effect measured in the cortex (Youssef et al., 2019) and one showed an increase in dopamine and serotonin levels when measured in the striatum (Shi et al., 2017).

5.2. Motor function

The effect of CB2R activation has been studied on motor function, either as a marker of functional recovery under pathological conditions, as a proper object of study or as a control when measuring other behavioral readouts (Supplementary Table 7). When peripherally administered, CB2R agonists tend to lower locomotor activity in healthy rodents in most of the reported studies (Cortez et al., 2022; Liu et al., 2017; Onaivi et al., 2008; Spiller et al., 2019; Valenzano et al., 2005; Xi et al., 2011), whereas administration of CB2R specific inverse agonists either had no effect on locomotion (Adamczyk et al., 2012; Li and Kim, 2016b; Martín-Sánchez et al., 2019; Viveros-Paredes et al., 2017a) or enhanced it (Onaivi et al., 2008). However, basal motor activity in mice overexpressing CB2R was similar to that of WT mice as measured in open field tasks (Aracil-Fernández et al., 2012; Li and Kim, 2017) and decreased in CB2R KO mice (Ortega-Alvaro et al., 2011). Intranigral microinjection of a CB2R agonist induced contralateral turning in healthy rats (Sánchez-Zavaleta et al., 2018). The fact that CB2R modulations mediate effects on motor activity in healthy animals, i.e. in non-inflammatory contexts, and that locomotor activity is increased when CB2R is specifically deleted in dopaminergic neurons (Canseco-Alba et al., 2019; Liu et al., 2017) demonstrate that CB2R can act directly on neuronal activity.

Under pathological conditions, treatment with CB2R agonists enhanced functional recovery in models of ALS (Espejo-Porras et al., 2019), high fat diet (Youssef et al., 2019), intracerebral hemorrhage (Li et al., 2018), spinal cord injury (Adhikary et al., 2011; Latini et al., 2014), TBI (Braun et al., 2018; Elliott et al., 2011; Magid et al., 2019), stroke (Yu et al., 2015), LPS-induced sickness behavior (Sahu et al., 2019a), chronic mild stress (Onaivi, 2006) and PD (He et al., 2020; Palomo-Garo et al., 2016; Shi et al., 2017; Viveros-Paredes et al., 2017a; Yu et al., 2021). In addition, motor impairments were worsened with CB2R inverse agonist in a model of stroke (Bravo-Ferrer et al., 2017) and when CB2R gene was deleted in models of HD (Palazuelos et al., 2009) and ALS (Rodríguez-Cueto et al., 2021). Among the 33 studies that demonstrated an effect of CB2R modulation on motor function, 12 showed a concurrent anti-inflammatory effect in the different regions of interest (Adhikary et al., 2011; Braun et al., 2018; Elliott et al., 2011; Espejo-Porras et al., 2019; Li et al., 2018; Magid et al., 2019; Reiner et al., 2014; Rodríguez-Cueto et al., 2021; Sahu et al., 2019b; Viveros-Paredes et al., 2017b; Youssef et al., 2019; Yu et al., 2015) and four showed

effects on neuronal functions (Sánchez-Zavaleta et al., 2018; Xi et al., 2011; Yu et al., 2021; Zhang et al., 2017).

5.3. Learning and memory

CB2R signaling seems to play an important regulatory role in learning and memory (Supplementary Table 8). Acute systemic administration of CB2R agonists to healthy WT rodent was shown to enhance recognition memory (Oliveira et al., 2016), spatial learning (Tchekalarova et al., 2018) and aversive memory consolidation (García-Gutiérrez et al., 2013; Kruk-Slomka et al., 2022, 2016). Beside CB2R pharmacological activation, genetic manipulation of CB2R further highlights its implication in learning and memory. Deletion of CB2R in mice disrupted consolidation of short and long term aversive memories (García-Gutiérrez et al., 2013; Ortega-Alvaro et al., 2011). CB2R is also involved in different hippocampus-dependent memory mechanisms, as its deletion impaired contextual fear memory (Li and Kim, 2016b; Wang et al., 2018) and either enhanced or decreased spatial memory depending on the task (Supplementary Table 8), without impacting cued fear memory (Li and Kim, 2016b). Furthermore, cell-specific genetic models made it possible to pinpoint specific cellular actors of CB2R-mediated memory enhancement. Microglia-specific overexpression of CB2R in the CA1 enhanced contextual fear memory while overexpression in pyramidal neurons or interneurons did not exert any effect on memory. Conversely, CA1 pyramidal cell-specific deletion improved performances in spatial memory task and microglia-specific deletion impaired contextual fear memory while enhancing novelty memory (Li and Kim, 2017).

Pharmacological manipulation of CB2R in pathological conditions can alleviate cognitive decline. Chronic systemic administration of CB2R specific agonists protected memory performances in different genetic and pharmacologic rodent models of AD (Aso et al., 2013; Fakhfoury et al., 2012; Jayant et al., 2016; Li et al., 2019a; Martín-Moreno et al., 2012; Wu et al., 2013, 2017), age-related cognitive decline (Lindsey et al., 2019), stroke (Ronca et al., 2015), HIV-induced neuronal injury (Wang et al., 2022), high fat diet-induced (Youssef et al., 2019) and surgery-induced (Sun et al., 2017) cognitive impairment, schizophrenia (Cortez et al., 2022), okadaic acid-induced neurodegeneration (Çakır et al., 2019), sepsis-induced encephalopathy (Yang et al., 2022), and vascular dementia (Lou et al., 2017; Luo et al., 2018a). Intra-CA1 GP1a microinjection resulted similarly in enhanced memory consolidation in a step-through task in a D-AP5 (selective NMDA receptor antagonist)-induced memory impairment rat model (Nasehi et al., 2017). Conversely, inverse agonists administration decreased cognitive abilities in healthy animals (García-Gutiérrez et al., 2013; Nasehi et al., 2017) and worsened cognitive deficits in rodent models of vascular dementia (Luo et al., 2018a) and D-AP5-induced (Nasehi et al., 2017) and surgery-induced cognitive impairments (Sun et al., 2017). Cognitive impairments were worsened when CB2R was deleted in models of aging (Komorowska-Müller et al.,

2021b) and isoflurane-induced cognitive decline (Li et al., 2021) but improved in models of AD (Galán-Ganga et al., 2021; Schmöle et al., 2018, 2015). It is to note that CB2R KO mice displayed AD-like tau hyperphosphorylation alongside their cognitive impairments (Wang et al., 2018).

Of the 34 studies that demonstrated an effect of CB2R modulation on memory and/or learning, 16 showed a concomitant immunomodulatory effect in the hippocampus and/or the cortex in pathological contexts (Aso et al., 2013; Çakır et al., 2019; Fakhfoury et al., 2012; Jayant et al., 2016; Li et al., 2021, 2019b; Luo et al., 2018b; Martín-Moreno et al., 2012; Schmöle et al., 2018, 2015; Sun et al., 2017; Wang et al., 2022; Wu et al., 2017, 2013; Yang et al., 2022; Youssef et al., 2019) and two showed protection of hippocampal long-term potentiation (Wu et al., 2017, 2013).

5.4. Mood

Chronic peripheral administration of CB2R agonists produced different effects on anxiety and depressive-like behavior in healthy rodents depending on the behavioral task (García-Gutiérrez et al., 2012; Onaivi et al., 2008; Valenzano et al., 2005; Verty et al., 2015) (Supplementary Table 9). CB2R pharmacological activation under pathological conditions counteracted anxiety- and/or depression-like behaviors induced by chronic stress (Hwang et al., 2020; Onaivi et al., 2008), neuropathic pain (Cabañero et al., 2020), LPS (Sahu et al., 2019a), high-fat diet (Youssef et al., 2019), sepsis-induced encephalopathy (Yang et al., 2022) and TBI (Braun et al., 2018). Interestingly, treatment with inverse agonists also reduced the basal level of anxiety in healthy laboratory-reared rodents (García-Gutiérrez et al., 2010; García-Gutiérrez and Manzanares, 2011) and anxiety and depression-like traits in models of anxiety (García-Gutiérrez and Manzanares, 2011; Ten-Blanco et al., 2022b), orexin-induced fear extinction deficit (Ten-Blanco et al., 2022a) and also TBI (Reiner et al., 2014).

Transgenic mice specifically overexpressing CB2R in the central nervous system exhibited an endophenotypic resistance to acute and chronic anxiogenic- and depression-like stimuli (García-Gutiérrez et al., 2010; García-Gutiérrez and Manzanares, 2011; Romero-Zerbo et al., 2012). In contrast, CB2R KO mice displayed high vulnerability to stressful stimuli (Liu et al., 2017; Ortega-Alvaro et al., 2011). It is to note that these phenotypes were not observed when CB2R overexpression or deletion was specifically induced in CA1 cells (Li and Kim, 2017). CB2R genetic deletion either induced anxiety-like behavior (Ortega-Alvaro et al., 2011) or had no effect (Li and Kim, 2016b) depending on CB2R KO mouse strain and test. Furthermore, depression-like behaviors are induced when CB2R is specifically deleted in dopaminergic neurons (Liu et al., 2017). However, in CB2R KO mice, mood dysregulation was lowered in aging (Komorowska-Müller et al., 2021b) and chronic mild stress (Liu et al., 2017) models.

Among the 19 studies that evidenced an effect of CB2R modulation on mood, 6 showed a simultaneous immunomodulatory effect (Braun et al., 2018; Hwang et al., 2020; Reiner et al., 2014; Sahu et al., 2019b; Yang et al., 2022; Youssef et al., 2019) and one showed an increase in field excitatory post-synaptic potential and a reduction in long term depression induced by LPS exposure in hippocampal slices (Hwang et al., 2020).

5.5. Reward and addiction

Accumulating evidence supports the potency of cannabinoids in treating drug addiction (Gonzalez-Cuevas et al., 2018) (Supplementary Table 10). Presently, the area of treating addiction is relatively unexplored with a current lack of viable therapies aside from lower doses or analogues of the offending substance. Coinciding with CB2R ability to modulate behaviors and mood, accumulating evidence supports the potency of cannabinoids in treating drug addiction.

5.5.1. Alcohol

CB2R appears to be involved in alcohol abuse as CB2R KO mice developed more robust alcohol conditioned place preference (CPP) and have a higher alcohol consumption than their WT littermates (Ortega-Álvarez et al., 2015; Powers et al., 2015). Intriguingly, specific deletion of CB2R in dopaminergic neurons reduced alcohol CPP (Liu et al., 2020). Chronic activation of CB2R signaling using specific agonists reduced alcohol rewarding behavior (Al Mansouri et al., 2014; Martín-Sánchez et al., 2019). Nevertheless, one single administration of CB2R agonist failed to modify alcohol intake and alcohol-CPP expression (Powers et al., 2015). It should be noted that different results were obtained under various stress conditions. CB2R pharmacological stimulation, in mice subjected to chronic mild stress, enhanced alcohol intake (Ishiguro et al., 2007; Onaivi et al., 2008). Moreover, CB2R invalidation in dopaminergic neurons, in mice exposed to subacute stress, displayed lower alcohol consumption as opposed to non-stressed mice (Liu et al., 2017). Taken together, these studies highlight the fact that CB2R may exert different roles depending on the cell type and physiological conditions.

5.5.2. Psychostimulants (Cocaine, nicotine, amphetamine)

The role of CB1R on the effects of psychostimulants has already been widely addressed (Chaperon et al., 1998; Peters et al., 2021; Solinas et al., 2008) but the role of CB2R is now receiving greater attention. Both peripheral, intra-accumbens and intra-VTA administration of CB2R selective agonists blocked cocaine-induced CPP (Canseco-Alba et al., 2019; Delis et al., 2016; Ignatowska-Jankowska et al., 2013; Lopes et al., 2020; Xi et al., 2011) and reduced cocaine self-administration (Xi et al., 2011; Zhang et al., 2015, 2014). This inhibition was reversed by the inverse agonist AM630 (Delis et al., 2016; Xi

et al., 2011; Zhang et al., 2014) and absent in CB2R KO mice (Xi et al., 2011; Zhang et al., 2015, 2014). Genetic manipulation studies support the inhibitory role of CB2R in cocaine-induced behavioral alteration as CB2R overexpressing mice display a conditioned place aversion and reduced cocaine self-administration (Aracil-Fernández et al., 2012), while specific deletion of the CB2R gene in dopaminergic neurons leads to an increased cocaine- (Liu et al., 2017), amphetamine- and methamphetamine-induced CPP (Canseco-Alba et al., 2019). These results bring a new insight on the involvement of CB2Rs expressed by dopaminergic neurons in the modulation of the reinforcing effects of cocaine, amphetamine and methamphetamine. However, CB2R activation seems to mediate opposite effects on consumption of nicotine, another psychostimulant, as both genetic invalidation and pharmacological blockade of CB2R abolished nicotine rewarding properties (Gamaledin et al., 2012; Ignatowska-Jankowska et al., 2013; Navarrete et al., 2013). In the case of nicotine, the CNS stimulant effect is associated with the cholinergic system. Therefore, CB2R seems to be differently involved in cholinergic and dopaminergic pathways. Taken together, these data support the notion that CB1R and CB2R have different and perhaps opposing roles in modulating cocaine's rewarding and psychomotor stimulant effects. A study using electrical intracranial brain-stimulation reward (BSR) paradigm provides support for this idea as animals treated with selective CB1R and CB2R receptor agonists produced significant BSR enhancement and inhibition, respectively (Spiller et al., 2019).

5.5.3. Opioids

Although few studies have examined the impact of CB2R ligands on opioid abuse so far, CB2R is known to interact with mu opioid receptors to attenuate chronic pain. Co-administration of a CB2R agonist alongside morphine produces synergistic increases in the anti-nociceptive effects of morphine (Grenald et al., 2017) (see section 5.6). In the same study, peripheral treatment with JWH-015, a CB2R agonist, decreased morphine-induced CPP. Hence, co-treatment with CB2R agonists allows significant synergistic inhibition of preclinical pain while reducing opioid-induced unwanted side effects. Further investigations are needed to understand the role of CB2R at the cellular and molecular level.

5.5.4. Other

Peripheral administration of CB2R agonist JWH-133 reduced food- (Martín-Sánchez et al., 2019) and sucrose- (Zhang et al., 2015) induced CPP in mice. The inhibitory effects of CB2R activation on reward circuits observed with alcohol and psychostimulants like cocaine appear therefore to be generalized to natural rewards such as food or sucrose. Nonetheless, the food-induced CPP was not diminished by a single dose of the CB2R inverse agonist AM630 unlike alcohol

Table 2. Co-occurrence of immunomodulatory and/or neuromodulatory effects with behavioral outcomes following modulation of CB2R activity. Inflammatory, neuronal or behavioral outcome following CB2R modulation is either enhanced (↗) or decreased (↘). The symbol “-” was used when the type of outcome has not been investigated by the corresponding study.

MODEL	CB2R MODULATION	BRAIN REGION	INFLAMMATORY OUTCOME	NEURONAL OUTCOME	BEHAVIORAL OUTCOMES	REF
Healthy (Mouse)	Pharmacological activation	nucleus accumbens	-	↘ extracellular DA	↘ basal and cocaine-enhanced locomotion	(Xi et al., 2011)
		VTA	-	↘ excitability	↘ cocaine self-administration	(Zhang et al., 2014)
		Substantia nigra	-	↘ autonomous firing rate	↗ motor function	(Yu et al., 2021)
Healthy (Rat)	Pharmacological activation	Substantia nigra	-	↘ K ⁺ -stimulated [³ H]-Glutamate release	Induction of contralateral turning (2–4 turns/min)	(Sánchez-Zavaleta et al., 2018)
Alzheimer's disease (APP/PS1 Tg Mouse)	Pharmacological activation	Cortex	↘ Inflammation	-	↗ recognition memory	(Aso et al., 2013)
		Cortex	↘ Inflammation	-	↗ recognition memory	(Li et al., 2019a)
		Hippocampus, entorhinal cortex	↘ Inflammation	↗ LTP	↗ memory	(Wu et al., 2017)
Alzheimer's disease (APP2576 Tg Mouse)	Pharmacological activation	Cortex	↘ Inflammation	-	↗ recognition memory	(Martín-Moreno et al., 2012)
Alzheimer's disease (icv STZ, Mouse)	Pharmacological activation	Brain	↘ Inflammation	-	↗ memory performance	(Jayant et al., 2016)
Alzheimer's disease (intrahippocampal Aβ ₁₋₄₀ , Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	↗ LTP, ↗ eEPSC amplitude	↗ spatial learning	(Wu et al., 2013)
Alzheimer's disease (intrahippocampal Aβ ₁₋₄₂ , Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ spatial learning	(Fakhouri et al., 2012)
Alzheimer's disease (APP/PS1 Tg Mouse)	Genetic blockade	Peri-plaques areas	↘ Inflammation	-	↗ spatial memory	(Schmöle et al., 2018)
		Brain	↘ Inflammation	-	↗ spatial memory at 6 months	(Schmöle et al., 2015)
Amyotrophic lateral sclerosis (Mouse)	Pharmacological activation	Ventral and dorsal horn	↘ Inflammation	-	↗ locomotor activity	(Espejo-Porras et al., 2019)
	Genetic blockade	Spinal cord	↗ Inflammation	-	↘ motor function	(Rodríguez-Cueto et al., 2021)
Chronic restraint stress (Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	↗ fEPSPs, ↘ LPS-induced intensification of LTD	↘ depression	(Hwang et al., 2020)
Cocaine (Mouse)	Pharmacological activation	Nucleus accumbens	-	↘ cocaine-enhanced extracellular DA	↘ cocaine self-administration (dose-dep), ↘ cocaine's rewarding efficacy.	(Xi et al., 2011)
Diet-induced inflammation (Rat)	Pharmacological activation	Prefrontal cortex	↘ Inflammation	-	↘ visceral fat index, ↗ spontaneous locomotor activity, ↗ memory, ↘ anxiety and depression	(Youssef et al., 2019)
HIV-1 glycoprotein 120 induced neural injury (Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ learning and memory performance	(Wang et al., 2022)
Intracerebral Hemorrhage (Rat)	Pharmacological activation	Peri hematoma-brain	↘ Inflammation	-	↗ sensorymotor and balance function	(Li et al., 2018)
Isoflurane-induced inflammation (mouse)	Genetic blockade	Hippocampus	↗ Inflammation	-	↘ spatial learning and memory	(Li et al., 2021)
LPS-induced inflammation (Mouse)	Pharmacological activation	Brain	↘ Inflammation	-	↗ locomotor activity, ↘ anxiety, depression	(Sahu et al., 2019a)
Morphine (Rat)	Pharmacological activation	Nucleus accumbens	-	↘ morphine-enhanced extracellular DA	↘ Morphine-induced CPP, Alone: analgesic effect (↗ morphine-induced analgesia)	(Grenald et al., 2017)
Morphine-mediated hyperalgesia (Rat)	Pharmacological activation	Spinal Cord	↘ Inflammation	-	↘ Morphine-mediated thermal hyperalgesia and tactile allodynia	(Tumati et al., 2012)
Multiple sclerosis (Mouse)	Pharmacological activation	Lumbar spinal cord	↘ Inflammation	-	↘ mechanical hyperalgesia	(Alberti et al., 2017)
Neuropathic pain (Mouse)	Genetic blockade	Spinal cord	↗ Inflammation	-	↗ basal nociceptive response, ↗ thermal hyperalgesia, mechanical and thermal allodynia	(Racz et al., 2008)
	Pharmacological activation	Spinal cord	↘ Inflammation	-	Analgesic effect, ↘ mechanical and thermal hyperalgesia	(Klauke et al., 2014)
Okadaic acid-induced neurodegeneration (Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ spatial memory performance	(Çakır et al., 2019)
Parkinson's disease (Mouse)	Pharmacological activation	Substantia Nigra and striatum	↘ Inflammation	-	↘ MPTP-induced movement impairment, ↘ stride length impairment, ↘ balance impairment	(Viveros-Paredes et al., 2017a)
	Pharmacological activation	Striatum	-	↗ DA and 5-HT levels	Prevention of MPTP-induced weight loss, ↗ motor function	(Shi et al., 2017)

Retrovirus Infection-Induced Neuropathic Pain (Mouse)	Pharmacological activation	Dorsal root ganglia & lumbar spinal cord	↘ Inflammation	-	↘ allodynia (↘ mechanical hypersensitivity)	(Sheng et al., 2019)
Sepsis-induced encephalopathy (Mouse)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ recognition and spatial memory, ↘ anxiety	(Yang et al., 2022)
Spinal cord injury (Mouse)	Pharmacological activation	Spinal cord	↘ Inflammation	-	↗ motor function	(Adhikary et al., 2011)
Stroke (Rat)	Pharmacological activation	Ischemic cortex	↘ Inflammation	-	↗ Functional recovery	(Yu et al., 2015)
Surgery-induced cognitive impairment (Mouse)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ contextual fear memory	(Sun et al., 2017)
Traumatic Brain Injury (Mouse)	Pharmacological blockade	Optic tract	↘ Inflammation	-	↗ locomotor activity, ↘ depression, ↗ fear extinction, ↘ fear	(Reiner et al., 2014)
	Pharmacological activation	Cortex	↘ Inflammation	-	↗ locomotor performance, ↗ usage of forelimb	(Elliott et al., 2011)
	Pharmacological activation	Cortex	↘ Inflammation	-	↗ motor coordination, ↘ anxiety	(Braun et al., 2018)
	Pharmacological activation	Cortex and hippocampus	↘ Inflammation	-	↗ locomotor performance	(Magid et al., 2019)
Vascular dementia (Rat)	Pharmacological activation	Hippocampus	↘ Inflammation	-	↗ spatial memory	(Luo et al., 2018a)
	Pharmacological blockade	Hippocampus	↗ Inflammation	-	↘ spatial memory	(Luo et al., 2018a)

Abbreviations: 5-HT, serotonin ; CPP, conditioned place preference ; DA, dopamine ; EPSP, excitatory post-synaptic potential ; LPS, lipopolysaccharide ; LTD, long term depression ; LTP, long term potentiation ; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ; Ref, reference ; Tg, transgenic ; VTA, ventral tegmental area.

-induced CPP. In this regard, CB2R inactivation appears to specifically interfere with drug-induced CPP induction, but not when a natural reinforcer is presented, such as food.

Overall, these findings support brain CB2R involvement in drug reward and addiction and suggest that brain CB2R may constitute a new target in therapeutics development for the treatment of substance abuse. Among the 20 studies that demonstrated an effect of CB2R modulation on addiction and reward behaviors, three showed an effect on neuronal activity, namely on extracellular dopamine levels in the nucleus accumbens (Grenald et al., 2017; Xi et al., 2011) and on the excitability of dopaminergic neurons in the VTA (Zhang et al., 2014). Knowing that CB2R expression has been robustly shown in these neurons, these results suggest a direct effect of CB2R activation on their activity which results in a behavioral outcome.

5.6. Analgesia

A growing body of evidence suggests that CB2R plays a role in pain modulation (Supplementary Table 11). Systemic treatment with CB2R specific agonists in rodents promoted an analgesic effect by itself, or potentiated opioid-induced analgesia (Altun et al., 2015; Grenald et al., 2017; Valenzano et al., 2005). Depending on the pain assay, GP1a alone may exert analgesic effects or enhance analgesia when combined with morphine (Chen et al., 2019). Hence, using cannabinoids may reduce the dose of opioids needed for analgesia in certain pain conditions. In addition, morphine-mediated thermal hyperalgesia and tactile allodynia were reduced following systemic CB2R agonist administration, suggesting that CB2R activation may be useful to prevent the neuroinflammatory consequences of sustained morphine treatment (Tumati et al., 2012). Other CB2R agonists were also shown to exert analgesic effects when administered to healthy rodents

(Altun et al., 2015; Cortez et al., 2022; Grenald et al., 2017; Klauke et al., 2014; Valenzano et al., 2005).

In different pathologic rodent models, CB2R agonists also presented antinociceptive properties, such as in a chronic inflammatory pain model (Negrete et al., 2011), multiple sclerosis (Alberti et al., 2017), high-fat diet (Schmitz et al., 2016), neuropathic pain (Cabañero et al., 2020; Grenald et al., 2017; Ibrahim et al., 2003; Klauke et al., 2014; Sheng et al., 2019; Shiu et al., 2017; Valenzano et al., 2005), incisional and inflammatory (Valenzano et al., 2005) and post-operative pain (Grenald et al., 2017).

Genetic models of invalidation further support the antinociceptive potency of CB2R. In fact, basal nociceptive responses were enhanced in several behavioral tests in CB2R KO mice (Racz et al., 2008). Dopaminergic neurons may be differentially involved in mechanisms underlying various pain conditions, as the pain threshold was raised in the tail flick test but tended to be lowered in the hot plate test in mice with CB2R deletion in dopaminergic neurons (DAT-CB2R cKO mice) (Liu et al., 2020, 2017). Irradiated WT mice reconstituted with bone marrow (BM) cells from CB2R KO mice developed the same enhanced manifestations of neuropathic pain as CB2R KO animals, demonstrating the protective role of CB2R in BM-derived cells that are recruited to the spinal cord in the development of neuropathic pain (Racz et al., 2008).

Of the 17 studies that showed an effect of CB2R modulation on pain perception, five showed a concomitant immunomodulatory effect (Alberti et al., 2017; Klauke et al., 2014; Racz et al., 2008; Sheng et al., 2019; Tumati et al., 2012) and one showed an effect on extracellular dopamine levels measured in the nucleus accumbens (Grenald et al., 2017).

5.7. Seizure activity

CB1R modulation can improve seizure outcomes, but is accompanied by several psychotropic effects, limiting its potential as a therapeutic target (Kow et al., 2014; Pertwee, 2012). CB2R has received less attention for its role in seizure activity so far. The few studies that have directly examined the effect of modulating CB2R activity on seizure susceptibility have yielded inconsistent results (Supplementary Table 12). The CB2R agonist β -caryophyllene (BCP) decreases seizure frequency and spread in mice undergoing maximal electroshock seizures (Tchekalarova et al., 2018). BCP and HU308 were found to increase the latency to myoclonic jerks induced by PTZ and to lower the seizure threshold (Ghanbari et al., 2020; Oliveira et al., 2016). However, it is also reported that direct brain injection of the CB2R agonist, AM1241, increased seizure severity in rats (de Carvalho et al., 2016). Additionally, the CB2R agonists HU-308 and BCP had no effect on PTZ-induced seizures in young rodents (Huizenga et al., 2017; Tchekalarova et al., 2018). JWH-133 administration, following pilocarpine-induced status epilepticus, reduced mortality and increased the latent period for the first seizure attack (Cao et al., 2021). Overall, while there is evidence that modulating CB2R activity can affect seizure susceptibility, this relationship remains unclear, highlighting the impact of differences in study design, including species, seizure model, CB2R agonist and dosing (Supplementary Table 12). The use of genetic manipulation brought new insight into the role of CB2R in seizure activity. Deletion of CB2R in mice resulted in a higher severity score of handling induced seizures after alcohol consumption (Ortega-Álvaro et al., 2015), and a higher average Racine score in a 6 Hz seizure induction paradigm (Shapiro et al., 2019). Furthermore, both heterozygous and homozygous KO mice exhibited increased susceptibility to PTZ-induced seizures. Among double KO mice with both CB1R and CB2R deletions, 27.6% of mice exhibited handling induced seizures and 80% mice had at least 1 spontaneous electrographic seizure, but no seizure were recorded from CB2R KO mice (Rowley et al., 2017), suggesting a synergic role of both CB1R and CB2R. Administration of the CB2R inverse agonist, SR144528, in WT mice increased seizure susceptibility, suggesting that increasing CB2R expression or activity may grant seizure protection (Shapiro et al., 2019).

Of the studies listed in this review that investigated the effect of CB2R modulation on epileptic activity, none looked for a parallel effect on inflammation or on neuronal activity. To better understand the role of CB2R in seizure susceptibility, it is crucial that future studies take into account these potential effects on neuroinflammation, which is known to be involved in the occurrence of seizures and comorbidities of epilepsy (Vezzani, 2020), and to investigate possible effects on neuronal activity whose imbalance leads to seizure occurrence.

Given the broad involvement of CB2R in behavior, understanding brain CB2R signaling may provide new insights into treatments for brain disorders ranging from dementia to epilepsy and drug addiction. Nonetheless, the underlying mechanisms at a cellular and molecular level remain unclear. To date, studies using cell-specific genome-editing techniques are still scarce. Studies in DAT-CB2R cKO mice have already demonstrated the involvement of CB2R in dopaminergic neurons in motor activities, anxiety and depression-like behaviors and in the differential rewarding properties of alcohol and various psychostimulants (Canseco-Alba et al., 2019; Liu et al., 2017). CB2R expression in microglia or in CA1 pyramidal neurons was shown to be involved in contextual fear memory or in spatial working memory, respectively (Li and Kim, 2016b). Once identity of cells expressing CB2R in brain have been accurately established (Atwood and Mackie, 2010; Grabon et al., 2023), future studies using novel manipulations of CB2R expression in specific types or subtypes of cells in different brain regions will allow robust isolation of the CB2R's role in behavior.

6. Targeting CB2R in clinical trials

To date, only three of the CB2R agonists listed in this review have been included in clinical studies. β -caryophyllene was tested in a phase 2 trial for the treatment of pain related to osteoarthritis of the knee as a topical cream in 56 participants (NCT03152578). The safety evaluation of the MDA7 agonist tested in phase 1 (NCT04375436) supports feasibility in clinical use and is likely to be tested in further clinical studies (Foss et al., 2020). Finally, paeoniflorin - in combination with other compounds - has been tested for the treatment of rheumatoid arthritis (NCT01600521). Although not as effective as current disease-modifying antirheumatic drugs (methotrexate and leflunomide), paeoniflorin appears to be a safer option as a substitute for these drugs in long-term rheumatoid arthritis treatment when their toxicity is an issue (Chen et al., 2013).

7. Conclusion

Evidence has accumulated over the last decade showing the broad involvement of CB2R in the control of brain functions, particularly in behavior, through neuroimmune processes. Of the 100 studies included in this review that showed behavioral outcomes following CB2R modulation, 33 observed a concomitant modulation of the neuro-inflammatory state and nine showed changes in neuronal activity (Table 2). This suggests that CB2R dependent modulation of behavior is indeed mediated by immunomodulatory and/or neural mechanisms, either directly or indirectly. Highly expressed by resident microglial cells, and presumably leukocytes infiltrating the CNS, CB2R appears as a promising candidate in drug development for targeting immunomodulatory processes, in particular those mediating changes in the polarization of brain immune cells towards a pro-healing state. The findings of discrete CB2R expression by certain neuronal populations and direct

control of neuronal activity by CB2R may explain some modulations of behavior observed following CB2R activation. Further developments of new genetic models of inducible *cn2r* gene invalidation, restricted to certain cell populations, is crucial to decipher the multifactorial mechanisms of which the endocannabinoid system, and CB2R in particular, can influence brain function and behavior.

Competing Interests

The authors declare no competing interests.

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CB2 receptor in the CNS: From immune and neuronal modulation to behavior

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Supplementary Table 1 – *In vitro* evidence of CB2R neuroimmunomodulatory functions. Details on CB2R ligand treatments are provided, such as the concentration of the ligand, the time it was applied to the cell culture with respect to inflammatory challenge. Outcome is either enhanced (↗) or decreased (↘).

CHALLENGE	CELL LINE & MODEL	TREATMENT	OUTCOME	OTHER	REF
CB2R AGONISTS APPLIED BEFORE CHALLENGE					
CCL2	Primary monocytes (Human)	GP1a, JWH-133, O-1966 (10 μM), AM1241 (2 μM)	↘ Adhesion to BMVEC, ↘ monocytes migration, ↘ lamellipodia formation, ↘ BMVEC monolayer disruption	-	(Rom et al., 2013)
CCL2 or CCL3	Primary monocytes (Human)	JWH-015 (5-20 μM, 12h pre-challenge)	↘ monocytes migration (dose-dep), ↘ CCR2, CCR1	Reversed with SR144528 (1 μM)	(Montecucco et al., 2008)
IFN-γ	Primary cultured microglia (Mouse)	JWH-015, JWH-133, GP1a (10, 10 and 3 μM respectively, 2h pre-challenge)	↘ phosphorylation of STAT3/STAT1	-	(Sheng et al., 2019)
IL-1β	Cultured astrocytes (Human fetus)	WIN55,212-2 (0.3-10 μM, 24h pre-challenge)	↘ iNOS, NO, TNF-α, IL-1β, IL-6, CXCL10, MCP1, CCL5, CXCL8	Reversed with SR144528 (10 μM)	(Sheng et al., 2005)
	BV2 (Microglia, Mouse)	AM1241, JWH-015 (0.1 μM, 30 min pre-challenge)	↘ NF-κB, iNOS, ROS	-	(Ribeiro et al., 2013)
LPS	Primary cultured microglia (Rat)	Anandamide (1 μM, 30 min pre-challenge)	↘ IL-6, NO, ↗ IL-10	-	(Malek et al., 2015)
	Primary cultured microglia (Rat)	JWH-015 (0.01-1 μM, 2h pre-challenge)	↘ ADP-induced microglia migration(dose-dep)	Reversed with AM630 (1 μM)	(Romero-Sandoval et al., 2009)
	THP-1 (Monocytes, Human)	JWH-015 (1-10 μM, 30 min pre-challenge)	↘ IL-1β, TNF-α	-	(Klegeris et al., 2003)
LPS/IFN-γ	OLN-93, (Oligodendrocytes, Rat)	β-caryophyllene (0.1-50 μM) JWH-133 (1 μM, 24h pre-challenge)	↘ NO, ROS, TNF-α	Reversed with AM630 (1 μM)	(Askari and Shafiee-Nick, 2019a)
	Primary cultured Macrophages (Mouse)	JWH-133 (10 nM-5 μM, 5 min pre-challenge)	↘ IL-12 (dose-dep), ↗ IL-10	Reversed with SR144528 (1 μM)	(Correa et al., 2005)
MPP+	Primary cultured astrocytes (Rat)	JWH-133 (1 μM for 40 min pre-challenge)	↘ iNOS, COX2, TNF-α, IL-1β, DMT1	Reversed with AM630 (1 μM)	(Jia et al., 2020)
TNF-α	Primary monocytes (Human)	GP1a, JWH-133, O-1966 (10 μM), AM1241 (2 μM)	↘ Adhesion to BMVEC, ↘ monocytes migration, ↘ lamellipodia formation, ↘ BMVEC monolayer disruption	-	(Rom et al., 2013)
CB2R AGONISTS APPLIED DURING CHALLENGE					
Aβ ₁₋₄₀	Primary cultured microglia (mouse)	HU210, JWH-133, WIN55,212-2 (0.1 μM, 4h of co-treatment)	↘ microglial activation: ↘ rod-like morphology, ↘ TNF-α	-	(Ramirez et al., 2005)
	Primary cultured microglia (Rat)	JWH-133 (0.1 μM, 4h of co-treatment)	↘ TNF-α	-	(Ramirez et al., 2012)
Aβ ₁₋₄₂	C6 Glioma cell (Rat)	JWH-015 (1 μM, 24h of co-treatment)	↗ GFAP	-	(Esposito et al., 2007)
	Primary cultured microglia (Mouse)	JWH-015 (5 μM, 24h of co-treatment)	↘ TNF-α, NO	-	(Ehrhart et al., 2005)
sCD40L	BMVEC (endothelial cells, Human)	JWH-133, O-1966 (10 μM, 24h of co-treatment)	↘ “BBB” model permeability	-	(Persidsky et al., 2015)
CCL2	BMVEC (endothelial cells, Human)	JWH-133, O-1966 (10 μM, 24h of co-treatment)	↘ monocyte migration	-	(Persidsky et al., 2015)
CXCL2	Cultured neutrophils (Mouse)	JWH-133 (1 μM for 30 min co-treatment)	↘ chemotaxis	No effect in CB2R KO cells	(Murikinati et al., 2010)
	Primary cultured neutrophils (Mouse)	RO6871304 (0.01-1 μM, 30 min of co-treatment)	↘ neutrophil migration	No effect in CB2R KO neutrophils	(Porter et al., 2019)

IFN-γ	Primary cultured microglia (Mouse)	JWH-015 (5 μ M, 12h of co-treatment)	\searrow TNF- α , NO, CD40, JAK/STAT phosphorylation	-	(Ehrhart et al., 2005)
	Primary monocytes (Human)	JWH-015, JWH-133 (20 μ M, 10 μ M respectively, 24h co-treatment)	\searrow ICAM-1	Reversed with SR144528 (1 μ M)	(Montecucco et al., 2008)
LPS, IFN-γ	SIM-A9 (Microglia, mouse)	HU308 (2.5 μ M, 30 min of co-treatment)	\searrow NO, iNOS, TNF- α , IL-1 β , IL-6	Reversed with AM630 (1 μ M)	(Young and Denovan-Wright, 2022)
	Primary cultured microglia (Mouse)	JWH-133 (10-100 nM, 18h of co-treatment)	\nearrow IL-10	-	(Correa et al., 2010)
LPS	Mixed glial cells (Microglia and astrocytes, rat)	JWH-133 (1 μ M, 48h of co-treatment)	\searrow NO, IL-1 β	-	(Pan et al., 2020)
	Primary cultured microglia (Mouse)	Anandamide (5 μ M, 12h of co-treatment)	\searrow IL-1 β , TNF- α , IL-6, iNOS	Partially reversed with SR144528 (1 μ M)	(Ortega-Gutiérrez et al., 2005)
	Primary cultured microglia (Mouse)	β -caryophyllene, JWH-133 (0.2-25, 1 μ M respectively, 24h of co-treatment)	\searrow IL-1 β , TNF- α , PGE2, NO, iNOS, ROS, \nearrow IL-10, GSH, Arg-1	Reversed with AM630 (0.1 μ M)	(Askari and Shafiee-Nick, 2019b)
	Primary cultured microglia (Rat)	HU210, WIN55,212-2 (1-10 μ M, 2h of co-treatment)	\searrow TNF- α	Not reversed with SR144528 (10 μ M)	(Facchinetti et al., 2003)
	Primary cultured microglia (Rat)	JWH-015 (1 μ M, 1-2h of co-treatment)	\searrow TNF- α	-	(Romero-Sandoval et al., 2009)
MPP+	MDM (Monocyte-derived macrophages, Human)	JWH-133 (10 μ M, 24h of co-treatment)	\searrow CXCL10-11-19-5, CCR7, TNF- α , ICAM-1, CCL3, IP-10	-	(Persidsky et al., 2015)
	SH-SY5Y (neuroblastoma cells, Human)	β -caryophyllene (1-2.5 μ M, 24h of co-treatment)	\searrow ROS	-	(G. Wang et al., 2018)
S. pneumoniae serotype 3	Mixed glial cells (Microglia and astrocytes, rat)	JWH-133 (1 μ M, 48h of co-treatment)	\searrow NO, IL-1 β , IL-6, TNF- α	-	(Pan et al., 2020)
TNF-α	bEnd.3 (Endothelial cells, mouse)	JWH-133 (1 μ M for 20 min co-treatment)	\searrow neutrophils adhesion	No effect in CB2R KO cells	(Murikinati et al., 2010)
	BMVEC (endothelial cells, Human)	JWH-133, O-1966 (10 μ M, 24h of co-treatment)	\searrow iNOS, CXCL10-11, ICAM-1, IL-8, IL-15, IL-18, CCL2, CD40, MCSF-1	-	(Persidsky et al., 2015)
	HBMEC (endothelial cells, Human)	JWH-133, O-1966 (10 μ M, 4-24h of co-treatment)	\nearrow Occludin, claudin-5, \searrow monocyte/endothelium interaction, \searrow ICAM-1, VCAM-1	-	(Ramirez et al., 2012)
CB2R AGONISTS APPLIED AFTER CHALLENGE					
LPS/IFN-γ	N9 (Microglia, mouse)	AM1241 (5 μ M, 24h treatment, 1h post challenge)	\searrow IL-1 β , TNF- α , IL-6, iNOS, \nearrow IL-10, BDNF, GDNF, Arg-1	Reversed with AM630 (10 μ M)	(Ma et al., 2015)
LPS	C8B4 (Microglia, mouse)	HU308, JWH-133 (24h treatment, 1h post challenge)	\searrow CD16/32, \searrow CD206	-	(Presley et al., 2015)
Thrombin	Primary cultured microglia (Rat)	JWH-133 (4 μ M, 24h treatment, 24h post challenge)	\searrow MAPK pathway phosphorylation, Iba1 ⁺ p-ERK ⁺	Reversed with AM630 (1 μ M)	(Tang et al., 2015)
	Primary cultured microglia (Rat)	JWH-133 (4 μ M, 48h treatment, 24h post challenge)	\nearrow cAMP, p-PKA, Epac1	Reversed with AM630 (1 μ M)	(Tao et al., 2016)
CB2R INVERSE AGONISTS APPLIED BEFORE CHALLENGE					
IL-4 + IL-13	Primary cultured microglia (Rat)	AM630 (1 μ M, 30 min pre-challenge)	\searrow Arg-1	-	(Mecha et al., 2015)
LPS	BV2 (Microglia, mouse)	AM630, SR144528 (0.1 μ M, 30 min pre-challenge)	\searrow NF- κ B, iNOS, ROS	-	(Ribeiro et al., 2013)
	Primary cultured microglia (Rat)	AM630 (0.5 μ M, 24h treatment 30 min pre-challenge)	\nearrow IL-1 β , IL-18, TNF- α	-	(Malek et al., 2015)
	Primary cultured microglia (Rat)	SMM-189 (10-40 μ M, 15 min pre-challenge)	\searrow IL-1 β , PGE2	-	(Yu et al., 2020)
CB2R INVERSE AGONISTS APPLIED DURING CHALLENGE					
Aβ₁₋₄₂	C6 Glioma cell (Rat)	SR144528 (1 μ M 12-24h of co-treatment)	\searrow GFAP	-	(Esposito et al., 2007)
IL-4	Immortalized microglia (Human)	SMM-189 (13.4 μ M, 24 of co-treatment)	\nearrow CD206	-	(Reiner et al., 2014)
LPS	Immortalized microglia (Human)	SMM-189 (13.4 μ M, 24 of co-treatment)	\searrow CD11b, CD45, CD80	-	(Reiner et al., 2014)
CB2R INVERSE AGONISTS APPLIED AFTER CHALLENGE					
LPS	C8B4 (Microglia, mouse)	SMM-189, SR144528 (0.15 μ M, 24h of treatment 1h post challenge)	\searrow CD16/32, \nearrow CD206	-	(Presley et al., 2015)
	Primary cultured microglia (Human)	SMM-189 (0.15 μ M, 24h of treatment 1h post challenge)	\searrow Eotaxin, IP10, TARC, MCP1, CCL4, \nearrow number of resting microglia	-	(Presley et al., 2015)
	Primary cultured microglia (Human)	SMM-189 (9.8 μ M, 18h of treatment 1h post challenge)	\searrow IFN- γ , IL-6, IL-10, IL-12p70, IL-8, MCP-1, CCL4, CCL17, CCL22, eotaxin-3	-	(Reiner et al., 2014)

Abbreviations : A β , amyloid beta ; ADP, adenosine diphosphate ; Arg-1, arginase 1 ; BBB, blood-brain barrier ; BDNF, brain-derived neurotrophic factor ; BMVEC, brain microvascular endothelial cells ; cAMP, cyclic adenosine monophosphate ; CB2R, cannabinoid receptor type 2 ; CCL, Chemokine (C-C motif) ligand ; CCR, C-C chemokine receptor ; CD, cluster of differentiation ; COX2, cyclooxygenase 2 ; CXCL, chemokine (C-X-C motif) ligand ; DMT1, divalent metal transporter 1 ; Epac1, Exchange Protein Directly Activated by cAMP Type 1 ; ERK, Extracellular signal-regulated kinases ; GDNF, Glial cell line-derived neurotrophic factor ; GFAP, Glial fibrillary acidic protein ; GSH, reduced glutathione ; HBMEC, human brain microvascular endothelial cells ; Iba1, ionized calcium-binding adapter molecule 1 ; ICAM, intercellular adhesion molecule ; IFN, interferon ; IL, interleukin ; iNOS, Inducible nitric oxide synthase ; JAK, janus kinase ; LPS, lipopolysaccharide ; MAPK, mitogen-activated protein kinase ; MCP1, monocyte chemoattractant protein 1 ; MCSF-1, macrophage colony-stimulating factor 1 ; MDM, monocyte-derived macrophage ; MPP+, 1-methyl-4-phenylpyridinium ; NF- κ B, nuclear factor-kappa B ; PGE2, prostaglandin E2 ; PKA, Protein kinase A ; Ref, reference ; ROS, *Reactive oxygen species* ; STAT, *signal transducer and activator of transcription* ; THP-1, Tohoku Hospital Pediatrics-1 Cells ; TNF, tumor necrosis factor ; VCAM, vascular cell adhesion molecule.

Supplementary Table 2 – *In vivo* evidence of CB2R neuro-immunomodulatory functions. Details on CB2R ligand treatments are provided, such as the dose of the ligand, treatment initiation and duration, administration route, with respect to inflammatory insult. Outcome is either enhanced (\nearrow), decreased (\searrow) or unchanged ($=$). In some studies, the specificity of the ligand used has been challenged by the use of CB2R KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), or the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TISSUE	OUTCOME	OTHER	REF
CB2R AGONISTS GIVEN BEFORE CHALLENGE					
Cerebral ischemia (MCAO, Mouse)	JWH-133 (1 mg/kg/day, IP microosmotic pump, 4h pre-insult, for >3 days)	Ischemic hemisphere	\searrow neutrophils recruitment, \searrow MPO activity, = TNF- α , IL-1 β , CXCL2	-	(Murikinati et al., 2010)
Chronic post-ischemia pain (Rat)	MDA7 (15 mg/kg, IP, 30 min pre-insult + daily for 14 days)	Spinal cord dorsal horn	\searrow CD11b, CXCR3	Reversed with AM630 (5 mg/kg, IP)	(Xu et al., 2016)
Focal ischemia/reperfusion (Mouse)	0-1966, 0-3853 (1 mg/kg, IV, 1h pre-insult)	Brain	\searrow leukocyte/endothelium interaction	-	(Zhang et al., 2007)
HIV-1 glycoprotein 120 induced neural injury (Rat)	WIN55,212-2 (3 mg/kg/day, IP, for 3 days pre-insult)	Hippocampus	\searrow IL-1 β , TNF- α , IL-6, CXCL10, \nearrow IL-10	Reversed with AM630 (1.5 mg/kg/day, IP)	(Wang et al., 2022)
Huntington's disease (Rat)	HU308 (5 mg/kg, IP, 20 min pre- and 2h post insult)	Striatum	\searrow TNF- α , = SOD1, SOD2	-	(Sagredo et al., 2009)
LPS-induced inflammation (Mouse)	1-phenylisatin (20 mg/kg, PO, 1h pre-insult)	Brain	\searrow TNF- α , \nearrow GSH, catalase, SOD	-	(Sahu et al., 2019)
MDMA (ecstasy) induced inflammation (Rat)	JWH-015 (2.4 mg/kg, IP, 2 days, 1 day and 30 min pre-insult)	Hypothalamus & PFC	\searrow IL-1 β , = CD11b	Reversed with AM630 (3 mg/kg, IP)	(Torres et al., 2010)
	JWH-015 (2.4 mg/kg, IP, 2 days, 1 day and 30 pre-+ 6h post-insult)	Hypothalamus & PFC	\searrow CD11b	Reversed with AM630 (3mg/kg, IP)	(Torres et al., 2010)
Neonatal stroke (Rat)	JWH-133 (1.5 mg/kg, IP, 1h pre-insult)	Peri-hematoma brain	\searrow TNF- α , \searrow number of Iba1 ⁺ cells	-	(Tang et al., 2016)
Paclitaxel-induced inflammation (Rat)	MDA7 (15 mg/kg, IP, 15 min pre-insult and for 4 days)	Spinal dorsal horn (L4-L5)	\searrow Iba1 immunostaining intensity, \searrow IL-6, \nearrow IL-10	-	(Wu et al., 2019)
Parkinson's disease (Mouse)	JWH-133, WIN55,212 (10 μ g/kg/day, IP, 2 days pre- insult + for 8 days post-insult)	Substansia Nigra	\searrow IL-1 β , TNF- α , iNOS, \searrow CCL3, CCL4, MCP-1, CXCL10, CCL5, \searrow T-cells and macrophages infiltration, \searrow number of MAC1 ⁺ cells, \searrow GFAP, MPO, \searrow BBB permeability	Reversed with AM630 (20 μ g/kg/day, IP)	(Chung et al., 2016)
	β -caryophyllene (10 mg/kg, IP, 1/day for 5 days, 24h pre-insult)	Substansia Nigra and striatum	= TNF- α , \searrow IL-6, IL-1 β \searrow number of Iba1 ⁺ and GFAP ⁺ cells	Reversed with AM630 (3 mg/kg, IP)	(Viveros-Paredes et al., 2017)
Parkinson's disease (Rat)	β -caryophyllene (50 mg/kg/day, IP, for 4 weeks and 30 min pre-insult)	Midbrain	\searrow TNF- α , IL-6, IL-1 β , NF- κ B p65, iNOS, COX-2, \nearrow GSH, catalase, SOD, \searrow Iba1, \searrow GFAP	Partially reversed with AM630 (1 mg/kg, IP)	(Javed et al., 2016)
PTZ-induced seizure (Rat)	HU308 (3 mg/kg, IP, 30 min pre-insult)	Dorsal hippocampus and neocortex	\searrow TNF- α , IL-6 (hippocampus only)	-	(Karan et al., 2021)
Spinal cord ischemia (Rat)	JWH-133 (1 mg/kg, IP, 1h pre-insult)	Spinal cord	\searrow TLR4, MMP9, MyD88, NF- κ B p-65, \searrow GFAP, \searrow BBB permeability, \nearrow Zonula occludens-1	Reversed with AM630 (1 mg/kg, IP)	(Jing et al., 2020)
Theiler's virus induced demyelination disease (Mouse)	2-AG (5 mg/kg, IP, 48h and 24h pre-insult)	Cortex	\searrow Iba1 ⁺ area, \searrow CSF1R, TNF- α , iNOS	Reversed with AM630 (2 mg/kg, IP)	(Mecha et al., 2018)
CB2R AGONISTS GIVEN DURING CHALLENGE					
AMPA-induced retina inflammation (Rat)	WIN55,212 (10 ⁻⁷ to 10 ⁻⁴ M, intravitreal)	Retina	\searrow number of Iba1 ⁺ cells	Reversed with AM630 (0.1 mM, intravitreal)	(Spyridakos et al., 2021)
Chronic restraint stress (Rat)	β -Caryophyllene (25-100 mg/kg, IP, daily for 28 days)	Hippocampus	\searrow COX-2, \nearrow BDNF	-	(Hwang et al., 2020)
EAE (Mouse)	β -Caryophyllene (50 mg/kg, PO, twice a day, from day 0 to 30 post-insult)	Lumbar spinal cord	\searrow Iba1 ⁺ area, \searrow iNOS	-	(Alberti et al., 2017)
High-Fat Diet (Mouse)	HU308 (5 μ g/day for 2 weeks, icv)	Hypothalamus	\searrow Iba1 ⁺ cells in the hypothalamic arcuate, \nearrow Iba1 ⁺ cells and GFAP ⁺ in the VMH, = STAT3 and ERK phosphorylation	-	(Rorato et al., 2022)
LPS-induced inflammation (Mouse)	JWH-133, 0-1966 (10 and 5 mg/kg respectively, IP)	Brain	\searrow BBB permeability, \searrow leukocyte/endothelium interaction, \searrow ICAM-1	Reversed with SR144528 (10 mg/kg, IP) and in KO mice (Deltagen)	(Ramirez et al., 2012)
Morphine-mediated hyperalgesia (Rat)	AM1241 (0.1-2.5 mg/kg, IP, 2/day for 6 days)	Spinal Cord	\searrow IL-1 β , TNF- α , \searrow CD11b, \searrow GFAP (dose dep)	-	(Tumati et al., 2012)
CB2R AGONISTS GIVEN AFTER CHALLENGE					
Alzheimer's disease (icv STZ, Mouse)	1-phenylisatin (10 mg/kg/day, PO, from day 1 for 30 days post-insult)	Brain	\searrow MPO, \nearrow AChE	-	(Jayant et al., 2016)
Alzheimer's disease (intracortical A β ₁₋₄₂ , Rat)	JWH-015 (5mg/kg, IP, 3-, 5- and 7-days post-insult)	Hippocampus	\nearrow GFAP	-	(Esposito et al., 2007)
Alzheimer's disease (intrahippocampal A β ₁₋₄₀ , Rat)	MDA7 (15 mg/kg/day, IP, from day 1 and for 14 days post-insult)	Hippocampus	\searrow IL-1 β , \searrow CD11b, \searrow GFAP	-	(Wu et al., 2013)
Alzheimer's disease (intrahippocampal A β ₁₋₄₂ , Rat)	WIN55,212 (10 μ g, intra hippocampal, 1h post-insult and repeated day 3, 5 and 7)	Hippocampus	\searrow TNF- α , NF- κ B	Partially reversed with SR144528 (70 μ g, intra hippocampal)	(Fakhfouri et al., 2012)

CO-induced cognitive memory (Rat)	WIN55,212-2 (1 mg/kg IP, 2h, 12h, and 24h post-insult)	Hippocampus	↓ number of Iba1 ⁺ cells, ↓ CD206 ⁺ cells, ↓ IL1R1, IL-33	Reversed with AM630 (1 mg/kg IP)	(Du et al., 2020)
Diet-induced inflammation (Rat)	β-Caryophyllene (30 mg/kg/D, PO, 9h post-insult for 4 weeks)	Prefrontal cortex	↓ TNF-α, iNOS, NF-κB	Partially reversed by AM630 (1 mg/kg, IP)	(Youssef et al., 2019)
Hemicerebellectomy (Rat)	JWH-015 (3 mg/kg, IP, daily for 7 days post-insult)	Pontine nuclei	↓ iNOS, ↓ number of CD11b ⁺ and GFAP ⁺ cells, ↓ ROS	Reversed with SR144528 (3 mg/kg, IP)	(Oddi et al., 2012)
HIV-1 encephalitis (Mouse)	GP1a (1 mg/kg/day, food, 1 day post-insult for 14 days)	Brain	↓ CD11b, TNF-α, = iNOS, IL-6, IL-1β, GFAP	-	(Gorantla et al., 2010)
Intracerebral Hemorrhage (Rat)	JWH-133 (1.5 mg/kg, IP, 1h post-insult)	Peri hematoma-brain	↓ IL-1β, TNF-α, iNOS, ↓ M2 polarization	-	(Lin et al., 2017)
	JWH-133 (1.5 mg/kg, IP, 1h post-insult)	Peri hematoma-brain	↓ TNF-α, IL-6, IL1-β, p-ERK, p38, = MCP1, ↓ number of Iba1 ⁺ cells, ↓ BBB permeability, ↓ Zonula occludens-1, claudin 5, ↓ MMP9	Reversed with SR144528 (3 mg/kg, IP)	(Li et al., 2018)
Multiple sclerosis (Mouse)	WIN55,212 (5 mg/kg/day, IP, 0-5 days post-insult)	Spinal cord	↓ IFN-α, IFN-β	-	(Croxford and Miller, 2003)
	WIN55,212 (5 mg/kg/day, IP, 26-31 days post-insult)	Spinal cord	↓ IL-1β, IL-6, TNF-α, IFN-γ	-	
	UCM707 (5 mg/kg/day, IP, 90 days post-insult, for 12 days)	Spinal cord	↓ microglial reactive morphology, CD11b	-	(Ortega-Gutiérrez et al., 2005)
	GP1a (5 mg/kg, IV, twice/week from day 0)	Spinal cord	↓ T cell infiltration (T _{H1} , T _{H17}), ↓ number of Iba1 ⁺ cells	-	(Kong et al., 2014b)
	GP1a (5 mg/kg, IV, twice/week from day 7)	Spinal cord	↓ TNF-α, IL-1β, IL-12p40, IL23p19, IFN-γ, IL-17, VCAM1, iNOS, CCL2, CCL5, CXCL10, ↓ T cell infiltration, ↓ number of Iba1 ⁺ cells	-	(Kong et al., 2014a)
Neuropathic pain (partial sciatic nerve ligation, Mouse)	β-caryophyllene (0.1-10 mg/kg daily, PO, starting 1-day post-insult)	Spinal cord	↓ Iba1, ↓ GFAP	-	(Klaue et al., 2014)
Okadaic acid-induced neurodegeneration (Rat)	JWH-133 (0.2 mg/kg, IP, for 13 days post-insult)	Hippocampus	↓ TNF-α, IL-1β	-	(Çakır et al., 2019)
Parkinson's disease (Intrastratial LPS injection, Mouse)	HU308 (5 mg/kg/day, IP, 16h post-insult and for 14 days)	Striatum	= TNF-α, IL-1β, ↓ iNOS, ↓ CD68 ⁺ cells	No effect in KO mice (Zimmer)	(Gómez-Gálvez et al., 2016)
Parkinson's disease (6-OHDA and L-DOPA, Mouse)	HU308 (1-5 mg/kg, IP, daily beginning 3 weeks post-insult)	Striatum	↓ Iba1 ⁺ cells, ↓ GFAP ⁺ cells, ↓ TNF-α, IL-1β	-	(Rentsch et al., 2020)
Pneumococcal Meningitis Model (Rat)	JWH-133 (1 mg/kg, 18h post-insult)	Cortex	↓ number of reactive microglial cells, ↓ resting microglia, ↓ neutrophil chemoattractant chemokines expression, ↓ IL-6, CCL3, CCL20	-	(Pan et al., 2020)
Retrovirus Infection-Induced Neuropathic Pain (Mouse)	JWH-015, JWH-133, GP1a, HU308 (5mg/kg/week, 5week post-insult)	Dorsal root ganglia & lumbar spinal cord	↓ macrophages and T infiltration (GP1a only, NS)	-	(Sheng et al., 2019)
Sepsis-induced encephalopathy (Mouse)	HU308 (2.5 mg/kg, IP, 30 post-insult and 1/day for 3 days)	Hippocampus	↓ IL-1β, CD68	-	(Yang et al., 2022)
Sepsis-induced encephalopathy (Rat)	JWH-133 (0.2-5 mg/kg, IP, immediately after insult)	Cortex and hippocampus	↓ TNF-α, IL-1β, IL-6, caspase-3, p-NF-κB	-	(Çakır et al., 2020)
Spinal cord injury (Mouse)	0-1966 (5 mg/kg, IP 1h+24h post-insult)	Spinal cord	= TNF-α, IL-1β, ↓ IL-23p19, IL-23R, TLR1, TLR4, TLR6, TLR7, CXCL9, CXCL11 ↓ IL-10, CCL2, CXCL1, ↓ Neutrophil and monocytes infiltration (but NS), ↓ number of Iba1 ⁺ cells	-	(Adhikary et al., 2011)
Stroke (Mouse)	JWH-133 (1.5 mg/kg, IP, 10 min post-insult)	Peri infarct-brain	= IL-1β, ↓ TNF-α, IL-6, IL-12, iNOS, TGF β, Ym1, IL-10, CCL5, MCP1, MIP1 α, ↓ Iba1 ⁺	-	(Zarruk et al., 2012)
Stroke (Rat)	AM1241 (2.5 mg/kg, IP, 2 days and 5 days post insult)	Ischemic cortex	↓ T-cell infiltration (CD4, CD8), ↓ Iba1 ⁺	-	(Yu et al., 2015)
Stroke (Neonatal, Rat)	JWH-133 (1.5 mg/kg, IP, 6h post-insult)	Peri hematoma-brain	↓ TNF-α, iNOS, p-ERK, ↓ number of Iba1 ⁺ cells	Reversed with AM630 (1 mg/kg, IP)	(Tang et al., 2015)
	JWH-133 (1 mg/kg, IP, 1h post-insult)	Peri hematoma-brain	↓ IL-1β, TNF-α, INF-γ, ↓ IL-4, IL-10, BDNF, ↓ Iba1 ⁺ CD68 ⁺ cells, ↓ M2 polarization	Reversed with AM630 (1 mg/kg, IP)	(Tao et al., 2016)
Surgery-induced cognitive impairment (Mouse)	JWH-133 (2 mg/kg/day, IP, immediately after insult)	Hippocampus, PFC	↓ IL-1β, TNF-α, ↓ MCP1, ↓ CD11b	-	(Sun et al., 2017)
Traumatic Brain Injury (CCI, Mouse)	0-1966 (5 mg/kg, IP, 1h+24h post-insult)	Cortex	↓ number of Iba1 ⁺ activated cells	-	(Elliott et al., 2011)
	0-1966, JWH-133 (5 and 1 mg/kg IP, respectively, 2h + 18h post-insult)	Cortex	↓ iNOS, TNF-α, ↓ BBB permeability	-	(Amenta et al., 2014)
	GP1a (1-5 mg/kg, IP, 10 min post-insult)	Cortex	↓ iNOS, TNF-α, IL-1β, IL-6, ↓ CCL2, CXCL10, ↓ IL-10, Arg-1, ↓ macrophage infiltration, ↓ M2 polarization (dose dep)	-	(Braun et al., 2018)
Traumatic Brain Injury (CCI, Rat)	JWH-133 (1.5 mg/kg, IP, 1h post-insult)	Cortex	↑ M2 microglial polarization	Reversed with SR144528 (3 mg/kg, IP)	(Li et al., 2022)
Traumatic brain injury (CHI, Mouse)	HU914 (0.1-10 mg/kg, IP, 1h post-insult)	Cortex and hippocampus	↓ TNF-α (hippocampus only)	-	(Magid et al., 2019)
Uveitis (Mouse)	HU308 (1.5%, topic, 15 min post-insult)	Eye	↓ neutrophil infiltration, ↓ endothelium adhering leukocytes	No effect in KO mice (Deltagen)	(Toguri et al., 2018)
	RO6871304, RO6871085 (1.5%, topic), HU910 (3 mg/kg, IV) immediately after insult	Eye	↓ endothelium adhering leukocytes	No effect in KO mice (Deltagen)	(Porter et al., 2019)

Uveitis (Rat)	HU308 (1.5%, topic, 15 min post-insult)	Eye	∖ TNF- α , IL-1 β , IL-6, IFN- γ , IL-10, NF- κ B, AP-1, ∖ CCL5, CXCL2, ∖ endothelium adhering leukocytes, = VCAM, ICAM	Reversed with AM630 (2.5 mg/kg, IV)	(Toguri et al., 2014)
Vascular dementia (Rat)	Paeoniflorin (40 mg/kg/day, IP, from day 15 post-insult for 25 days)	Hippocampus	∖ p-mTOR, p-I κ B α , pNF- κ B p-p65, ∖ number of Iba1 ⁺ cells, ∖ M2 polarization	Reversed with AM630 (3 mg/kg, IP)	(Luo et al., 2018)
CHRONIC CB2R ACTIVATION					
Alzheimer's disease (APP2576 Tg Mouse)	JWH-133 (0.2 mg/kg/day, drinking water from 7 months)	Cortex	∖ TNF- α , COX2, = IL-6, ∖ number of Iba1 ⁺ cells, = GFAP	-	(Martín-Moreno et al., 2012)
Alzheimer's disease (APP/PS1 Tg Mouse)	JWH-133 (0.2 mg/kg/day for 5 weeks, drinking water from 3 months)	Cortex	∖ IL-1 β , TNF- α , IL-6, IL-10, SOD1, SOD2, ∖ number of Iba1 ⁺ cells, =GFAP	-	(Aso et al., 2013)
	JWH-015 (0.15 mg/kg/day, IP, from 8 months, for 8 weeks)	Cortex	∖ Iba1 ⁺ , ∖ M2 polarization	-	(Li et al., 2019)
	MDA7 (14 mg/kg, IP, ½ day, from 3- to 8-month-old)	Hippocampus, entorhinal cortex	∖ Iba1	-	(Wu et al., 2017)
Amyotrophic lateral sclerosis (Mouse)	HU-308 (5 mg/kg, IP, daily from 65 to 90 days old)	Ventral and dorsal horn	∖ activated GFAP ⁺ cells, ∖ Iba1 ⁺ cells	-	(Espejo-Porras et al., 2019)
Sub-chronic stress-induced inflammation (Mouse)	JWH-133 (2 mg/kg, IP, daily)	Frontal cortex	∖ TNF- α , iNOS, PGE ₂	No effect in KO mice (Zimmer)	(Zoppi et al., 2014)
Spontaneous hypertension-induced inflammation (Rat)	JWH-133 (1 mM, 10 μ L, icv, daily for 28 days)	Rostral ventrolateral medulla	∖ TNF- α , IL-6, IL-1 β	Reversed with AAV2-r-CB2shRNA infusion	(Shi et al., 2020)
PRE-INDUCTION CB2R BLOCKADE					
Stroke (Neonatal, Rat)	AM630 (1 mg/kg, IP, 1h pre-insult)	Peri hematoma brain	= IL-6, TNF- α , TGF- β , = number of Iba1 ⁺ cells	-	(Tang et al., 2016)
POST-INDUCTION CB2R BLOCKADE					
Alzheimer's disease (Intracortical Aβ 1-42, Rat)	SR144528 (5 mg/kg, IP, 3, 5 and 7D post-insult)	Hippocampus	∖ GFAP	-	(Esposito et al., 2007)
Surgery-induced cognitive impairment (Mouse)	AM630 (3 mg/kg/day, IP, immediately post-insult for 7 days)	Hippocampus & PFC	∖ TNF- α , IL-1 β , ∖ MCP1 (PFC only), ∖ CD11b	-	(Sun et al., 2017)
Status Epilepticus (Kainate, Mouse)	SMM-189 (6 mg/kg, IP, 1h post-insult)	Hippocampus & cortex	∖ IL-1 β , IL-6, TNF- α , CCL2, CCL3, CCL4, ∖ Iba1, GFAP	-	(Yu et al., 2020)
Traumatic Brain Injury (air blast injury, Mouse)	SMM-189 (6 mg/kg, IP, 2h post-insult and daily for 14 days)	Optic tract	∖ MHC class II	-	(Reiner et al., 2014)
Traumatic Brain Injury (CCI, Mouse)	SR144528 (5 mg/kg, IP, 2h and 18h post-insult)	Cortex	∖ TNF- α , = ICAM	-	(Amenta et al., 2014)
	AM630 (1-5 mg/kg, IP, 10 post-insult)	Cortex	= iNOS, TNF- α , IL-1 β , IL-6, CCL2, CXCL10, = monocyte infiltration, no effect on polarization	-	(Braun et al., 2018)
Uveitis (Rat)	AM630 (2.5 mg/kg, IV, 15 min post-insult)	Eye	∖ NF- κ B, = AP-1, ∖ TNF- α , IL-10, CXCL2, ∖ endothelium adhering leukocytes	-	(Toguri et al., 2014)
Vascular dementia (Rat)	AM630 (3 mg/kg/day, IP, day 15 post insult for 27 days)	Hippocampus	∖ p-mTOR, p-I κ B α , pNF- κ B p-p65, ∖ M1 polarization	-	(Luo et al., 2018)

Abbreviations : AAV2-r-CB2shRNA, adeno-associated virus expressing CB2-specific shRNA ; A β , amyloid beta ; AchE, Acetylcholinesterase ; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid ; AP-1, Activator protein 1 ; Arg-1, arginase 1 ; BBB, blood-brain barrier ; BDNF, brain-derived neurotrophic factor ; CB2R, cannabinoid receptor type 2 ; CCI, controlled cortical impact ; CCL, Chemokine (C-C motif) ligand ; CD, cluster of differentiation ; CHI, closed-head injury ; COX2, cyclooxygenase 2 ; CSF1R, Colony stimulating factor 1 receptor CXCL, chemokine (C-X-C motif) ligand ; CXCR, C-X-C chemokine receptor ; EAE, Experimental autoimmune encephalomyelitis ; ERK, Extracellular signal-regulated kinases ; GFAP, Glial fibrillary acidic protein ; GSH, reduced glutathione ; HIV, human immunodeficiency virus ; Iba1, ionized calcium-binding adapter molecule 1 ; ICAM, intercellular adhesion molecule ; ICV, intracerebroventricular ; IFN, interferon ; IL, interleukin ; IL1R1, Interleukin 1 receptor-like 1 ; iNOS, Inducible nitric oxide synthase ; IP, intra-peritoneal ; IV, intra-venous ; KO, knock-out ; LPS, lipopolysaccharide ; Mac1, Macrophage-1 antigen ; MCAO, middle cerebral artery occlusion ; MCP1, monocyte chemoattractant protein 1 ; MDA7, melanoma differentiation associated gene-7 ; MDMA, 3,4-methylenedioxy-N-methylamphetamine ; MHC, major histocompatibility complex, MMP9, Matrix metalloproteinase 9 ; MPO, Myeloperoxidase ; mTOR, mammalian Target of Rapamycin ; MyD88, myeloid differentiation primary response 88 ; NF- κ B, nuclear factor-kappa B ; NS, non-significant ; PGE2, prostaglandin E2 ; PFC, prefrontal cortex ; PO, per os ; PTZ, pentyleneetetrazole ; Ref, reference ; SOD, superoxide dismutase ; STAT, signal transducer and activator of transcription ; STZ, Streptozotocin ; Tg, transgenic ; TGF, transforming growth factor ; TLR, Toll-like receptor ; TNF, tumor necrosis factor ; VCAM, vascular cell adhesion molecule ; VMH, ventromedial hypothalamus.

Supplementary Table 3 – CB2R KO mice. Outcome from CB2R KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000), and the “Romero strain” generated with the cre-lox method (López et al., 2018)) is either enhanced (↗), decreased (↘) or unchanged (=) when compared to wild-type littermates.

CONDITION	ANIMAL MODEL	TISSUE	OUTCOME	REF
α-Syn fibril induced inflammation	Deltagen CB2R KO mice + Intra NAc Fibrillar α-Syn	Nucleus Accumbens	↗ microglial activation, ↗CD68, C3aR, ↗M1 polarization	(Feng et al., 2022)
Amyotrophic lateral sclerosis	Romero CB2R KO mice x A315T	Spinal cord	↗ GFAP, Iba1 intensity signal, = TNF-α, IL-1β	(Rodríguez-Cueto et al., 2021)
Alzheimer’s disease	Deltagen CB2R KO mice x J20 APP mice	Hippocampus	= Iba1	(Koppel et al., 2014)
	Zimmer CB2R KO mice x APP/PS1 mice	Brain	↘ TNF-α, CCL2, Iba1, = Arg-1, ↘ Macrophage infiltration	(Schmöle et al., 2015)
	Romero CB2R KO mice x 5xFAD mice	Hippocampus	= IL-1β, Iba1	(López et al., 2018)
	Zimmer CB2R KO mice x APP/PS1 mice	Peri-plaques areas	↘ microglial activation (morphological complexity)	(Schmöle et al., 2018)
	Romero CB2R KO mice x 5xFAD mice	Cortex	↘ Iba1	(Ruiz de Martín Esteban et al., 2022)
Age-related cognitive decline	Zimmer CB2R KO mice	Hippocampus	↗ Iba1, CD68, ↘ microglia soma size (18 months)	(Komorowska-Müller et al., 2021a)
Hypoxia-ischemia	Zimmer CB2R KO mice + carotid ligation	Brain	↗ GFAP, Iba1	(Kossatz et al., 2016)
Isoflurane-induced inflammation	Deltagen CB2R KO mice + Isoflurane exposure	Hippocampus	↗ Iba1, microglial branches, ↗ IL-6, TNF-α, iNOS, ↘ Ym1/2	(Li et al., 2021)
LPS-induced inflammation	Deltagen CB2R KO mice + LPS	Brain	= leukocyte/endothelium interaction	(Ramirez et al., 2012)
LPS+IFN γ-induced inflammation	Zimmer CB2R KO mice	Organotypic hippocampal slice cultures	↘ Iba1, CD68	(Reusch et al., 2022)
Multiple Sclerosis	Deltagen CB2R KO mice + experimental autoimmune encephalomyelitis	Spinal cord	↗ IL-1β	(Shao et al., 2014)
Neuropathic pain	Zimmer CB2R KO mice + sciatic nerve injury	Spinal cord	↗ GFAP, ↗ Iba1, activated phenotype	(Racz et al., 2008)
Parkinson’s disease	Zimmer CB2R KO mice + intrastriatal LPS injection	Substansia Nigra	↗ CD68	(Gómez-Gálvez et al., 2016)
Sub-chronic stress-induced inflammation	Zimmer CB2R KO mice	Frontal cortex	↗ TNF-α, CCL2, iNOS, PGE ₂	(Zoppi et al., 2014)
Traumatic Brain Injury	Deltagen CB2R KO mice + CCI injury	Cortex	↗ TNF-α, ICAM, ↗ iNOS, ↗ BBB permeability	(Amenta et al., 2014)
Uveitis	Deltagen CB2R KO mice + endotoxin induced uveitis	Eye	= neutrophil infiltration, ↗ endothelium adhering leukocytes	(Toguri et al., 2018)
	Deltagen CB2R KO mice + endotoxin induced uveitis	Eye	↗ endothelium adhering leukocytes	(Porter et al., 2019)

Abbreviations : α-Syn, α-synuclein ; Arg-1, arginase 1 ; BBB, blood-brain barrier ; C3aR, complement component 3a receptor ; CB2R, cannabinoid receptor type 2 ; CCI, controlled cortical impact ; CCL, Chemokine (C-C motif) ligand ; CD, cluster of differentiation ; GFAP, Glial fibrillary acidic protein ; Iba1, ionized calcium-binding adapter molecule 1 ; ICAM, intercellular adhesion molecule ; IFN, interferon ; IL, interleukin ; iNOS, Inducible nitric oxide synthase ; KO, knock-out ; LPS, lipopolysaccharide ; NAc, nucleus accumbens ; PGE₂, prostaglandin E₂ ; Ref, reference ; TNF, tumor necrosis factor.

Supplementary Table 4. *In vitro* effects of CB2R ligands. CB2R agonists are presented in green, CB2R inverse agonists are presented in red. Outcome following CB2R activation is either enhanced (\nearrow), decreased (\searrow) or unchanged (=).

TISSUE/CELLS	NEURONAL SUBTYPE	CB2R LIGAND (bath application)	OUTCOME	OTHER	REF
NEUROTRANSMITTERS RELEASE					
Hippocampus (Mouse)	GABA neurons (hippocampal synaptosomes)	WIN55,212-2, HU210 (0.3 μ M, 9 min)	\searrow evoked GABA release	-	(Andó et al., 2012)
Spinal Cord (Rat)	CGRP neurons (spinal cord slices)	AM1241 (1-300 nM, 10 min)	\searrow capsaicin induced CGRP release	Blocked by SR144528 (60 nM)	(Beltramo et al., 2006)
Substantia Nigra (Rat)	Glutamatergic neurons (substantia nigra slices)	GW833972A, GW405833, JWH-133 (1nM-1 μ M)	\searrow K ⁺ -stimulated [³ H]-Glutamate release (dose-dep)	Blocked by JTE-907 (100nM) and AM630 (200 nM)	(Sánchez-Zavaleta et al., 2018)
Dorsal striatum (Rat)	DA neurons (dorsal striatum slices)	GW833972A (100 nM)	\searrow K ⁺ -stimulated [³ H]-dopamine release (when D2 autoreceptors were blocked)	Blocked by AM630 (100 nM)	(López-Ramírez et al., 2020)
NEUROTRANSMITTER RECEPTORS EXPRESSION					
Neuronal cell culture	CLU213	GP1a (1 nM), JWH-133 (30 nM) for 24h	\nearrow 5-HT _{2A} expression	Blocked by AM630 (1 μ M)	(Franklin and Carrasco, 2012)
IONIC CURRENTS					
mPFC (Rat)	Layer II/III pyramidal neurons (mPFC slices)	JWH-133 (1 μ M, 2-6 min)	Cl ⁻ current evokation	-	(den Boon et al., 2014)
	Layer II/III pyramidal neurons (mPFC slices)	JWH-133 (1-5 μ M, 15 min)	\nearrow intracellular [Ca ²⁺]	-	(den Boon et al., 2012)
Retina (Rat)	Retinal ganglion cells (isolated neurons)	CB65 (500 nM), HU-308 (300nM)	= L-type Ca ²⁺ current amplitudes. \nearrow T-type Ca ²⁺ current amplitude	Blocked by AM630 (100 nM)	(Qian et al., 2017)
	Retinal ganglion cells (isolated neurons)	AM630 (100 nM)	No effect on [Ca ²⁺] currents.	-	(Qian et al., 2017)
VTA (Mouse)	DA neurons (VTA slices)	JWH-133 (1 μ M, 10 min)	\nearrow M-type K ⁺ current	Blocked by AM630 (10 μ M), No effect in KO mice (Zimmer strain)	(Ma et al., 2019)
MEMBRANE POTENTIAL					
mPFC (Rat)	Layer II/III pyramidal neurons (mPFC slices)	JWH-133 (1-5 μ M), HU310 (1 μ M, 15 min)	Transient delayed depolarization	Blocked by SCH.356036 (5 μ M). No effect in KO mice (Deltagen strain)	(den Boon et al., 2012)
VTA (Mouse)	DA neurons (single isolated neurons)	JWH-133 (1 μ M)	Hyperpolarization	Blocked by AM630 (1 μ M). No effect in KO mice (Zimmer strain)	(Zhang et al., 2014)
VTA (Rat)	DA neurons (single isolated neurons)	JWH-133 (1 μ M, 2 min)	Hyperpolarization	-	(Zhang et al., 2017)
EXCITABILITY					
mPFC (Rat)	Layer II/III pyramidal neurons (mPFC slices)	JWH-133 (1-5 μ M, 15 min)	\searrow Excitability	-	(den Boon et al., 2012)
	Layer II/III pyramidal neurons (mPFC slices)	SCH.356036 (5 μ M, 15 min)	\nearrow Excitability	No effect in KO mice (Deltagen strain)	(den Boon et al., 2012)
Red nucleus (Mouse)	RN glutamatergic magnocellular neurons (midbrain slices)	JWH-133 (0.01-1 μ M, 10 min)	\searrow Firing rate (dose dep)	Blocked by AM630 (1 μ M). No effect in KO mice (Zimmer strain)	(Zhang et al., 2021)
	RN GABAergic neurons (midbrain slices)	JWH-133 (0.01-1 μ M, 10 min)	= Firing rate	-	(Zhang et al., 2021)
SNC	DA neurons (SNC slices)	GW842166 (1 μ M)	\searrow autonomous firing rate	Blocked by AM630 pre incubation (10 μ M)	(Yu et al., 2021)
VTA (Mouse)	DA neurons (VTA slices)	JWH-133 (1-100 μ M, 10 min)	\searrow Firing rate (dose dep)	-	(Ma et al., 2019)
	DA neurons (single isolated neurons)	JWH-133 (1-10 μ M)	\searrow AP firing rate, \nearrow AP initiation, \searrow AP duration and \nearrow AHP = \searrow excitability	Blocked by AM630 (1 μ M). No effect in KO mice (Zimmer strain)	(Zhang et al., 2014)
	DA neurons (VTA slices)	GW405833 (10 μ M)	\searrow AP firing rate	Blocked by AM630 (1 μ M). No effect in KO mice (Zimmer strain)	(Zhang et al., 2014)
VTA (Rat)	DA neurons (single isolated neurons)	JWH-133 (1 μ M, 2 min)	\searrow AP firing rate, \nearrow AHP	-	(Zhang et al., 2017)
SYNAPTIC TRANSMISSION					
Cerebellum (Mouse)	Purkinje cells (cerebellum slices)	CB65, JWH-133 (0.1 μ M, 5 min)	= eEPSC amplitude, \searrow IPSC amplitude, \searrow post-synaptic GABA _A receptor-mediated currents	Reduced by SR144528 (0.5 μ M)	(Sadanandan et al., 2020)
Entorhinal cortex (Rat)	Layer II-V neurons (EC-hippocampal slices)	JWH-133 (50 nM)	\searrow sIPSC amplitude	Blocked by AM630 (50 nM)	(Morgan et al., 2009)
	Layer II-V neurons (EC-hippocampal slices)	JTE-907 (0.5-1 nM)	\nearrow sIPSC amplitude and frequency	-	(Morgan et al., 2009)
Hippocampus (Mouse)	CA3 pyramidal cells (hippocampal slices)	HU-308 (1 μ M, 10 min)	= eIPSC amplitude of DSI+ neurons, = fEPSPs	-	(Stempel et al., 2016)
	CA1 pyramidal cells (hippocampal slices)	SR144528 (0.2 μ M, 40-45 min)	No effect on fEPSPs amplitude	-	(Li and Kim, 2016a)
Hippocampus (Rat)	Hippocampal slices	β -Caryophyllene (50 μ M 100 min)	\nearrow fEPSPs, \searrow LPS-induced intensification of LTD	-	(Hwang et al., 2020)
	CA1 pyramidal cells (hippocampal slices)	JWH-133 (0.2 μ M, 7-10 days)	= mIPSCs and eIPSC amplitude and frequency, = eEPSC amplitude, \nearrow mEPSC frequency	Blocked by SR144528 (100 nM). No effect in KO mice (Deltagen strain)	(Kim and Li, 2015)
	CA1 pyramidal cells (hippocampal slices)	GP1a (10 nM)	\nearrow mEPSC frequency	-	(Kim and Li, 2015)
SYNAPTIC PLASTICITY					
Hippocampus (Mouse)	CA3 pyramidal cells (hippocampal slices)	HU-308 (1 μ M, 10 min)	Mimic AP-Driven long-lasting Hyperpolarization (= slow self-inhibition)	No effect in KO mice (Zimmer strain) nor in (Syn-)CB2R custom cKO mice.	(Stempel et al., 2016)

	CA3 pyramidal cells (hippocampal slices)	SR144528 (2-5µM, 10 min)	∩ AP induced long lasting hyperpolarization	-	(Stempel et al., 2016)
Somatosensory cortex (Mouse)	Layer II/III RNSCP interneurons (somatosensory cortex slices)	HU-308 (1µM, 10 min)	Mimic AP-Driven long-lasting Hyperpolarization	Blocked by SR144528 (1 µM), no effect in KO mice (Zimmer strain)	(Stumpf et al., 2018)
DENDRITIC SPINES					
Hippocampus (Rat)	CA1 pyramidal cells (hippocampal slices)	JWH-133 (200 nM), GP1a (10 nM, 7-10 days)	∧ dendritic spine density	Blocked by SR144528 (100 nM). No effect in KO mice (Deltagen strain)	(Kim and Li, 2015)

Abbreviations : 5-HT, 5-hydroxytryptamine receptor ; AHP, afterhyperpolarization ; AP, action potential ; CA1 and 3, Cornu ammonis 1 and 3 ; CB2R, CGRP, calcitonin gene-related peptide ; cKO, conditional knock-out ; DA, dopamine ; dose-dep, dose dependent ; DSI, depolarization-induced suppression of inhibition ; EC, entorhinal cortex ; eEPSC, evoked excitatory post-synaptic current ; EPSP, excitatory post-synaptic potential ; eIPSC, evoked IPSC ; fEPSPs , field EPSP ; GABA, gamma-aminobutyric acid ; IPSC, inhibitory post-synaptic current ; KO, knock-out ; LPS, lipopolysaccharide ; LTD, long term depression ; mEPSC, miniature EPSP ; mIPSC, miniature IPSC ; mPFC, medial prefrontal cortex ; Ref, reference ; RNSCP, regular spiking non-pyramidal cells ; sIPSC, spontaneous IPSC ; SNc, substantia nigra compacta ; RN, red nucleus ; VTA, ventral tegmental area

Supplementary Table 5. *In vivo* effect of CB2R agonists. Outcome following CB2R activation is either enhanced (∧), decreased (∩) or unchanged (=).

CONDITION	TISSUE	NEURONAL SUBTYPE	TREATMENT	OUTCOME	OTHER	REF
NEUROTRANSMITTERS RELEASE						
Healthy (Mouse)	NAc	DA neurons	JWH-133 (3-20mg/Kg IP or 100µg/nostril IN or 1-1000 µM local intra NAc perfusion)	∩ extracellular DA (dose dep)	Blocked by AM630 (10 mg/kg IP). No effect in KO mice (Zimmer strain)	(Xi et al., 2011)
Healthy (Rat)	NAc	DA neurons	JWH-133 (10-20 mg/kg, IP)	= extracellular DA	-	(Zhang et al., 2017)
Cocaine self administration (Mouse)	NAc	DA neurons	JWH-133 (3-20mg/Kg IP, 30 prior to cocaine self admin)	∩ cocaine-enhanced extracellular DA (dose dep)	Blocked by AM630 (10 mg/kg IP). No effect in KO mice (Zimmer strain)	(Xi et al., 2011)
Ischemia (MCAO, rat)	Dorsal hippocampus	Glutamatergic neurons	JWH-133 (50-100 µM, intra-dorsal hippocampus infusion)	∩ ischemia-enhanced extracellular glutamate (dose-dep)	Blocked by AM630 (50µM)	(Zheng et al., 2015)
Morphine (Rat)	NAc	DA neurons	JWH-015 (1 mg/kg, IP, 1h before morphine injection)	∩ morphine-enhanced extracellular DA	-	(Grenald et al., 2017)
PD (MPTP, mouse)	Striatum	DA and serotonin neurons	AM1241 (0.75 to 12 mg/kg), IP, daily for 12 days starting 24 h after the last MPTP injection)	∧ DA and 5-HT levels (dose-dep)	-	(Shi et al., 2017)
IONIC CURRENTS						
Spinal nerve ligation (Rat)	Spinal Cord	Deep convergent dorsal horn neurons	JWH-133 (8-486 ng/50 µL, local spinal administration)	∩ capsaicin evoked [Ca ²⁺] _i increase	Blocked by SR144528 (1 ng/50 µL)	(Sagar et al., 2005)
MEMBRANE POTENTIAL						
Physio (Mouse)	Hippocampus	CA3 pyramidal cells	HU-308 (10mg/kg, 1 injection after 1-hour baseline)	Hyperpolarization	No effect in KO mice (Zimmer strain) nor in Syn-CB2R custom cKO mice.	(Stempel et al., 2016)
EXCITABILITY						
Healthy (Mouse)	Hippocampus	CA3 pyramidal cells	HU-308 (10mg/kg, 1 injection after 1-hour baseline)	∩ spike probability	No effect in KO mice (Zimmer strain) nor in Syn-CB2R custom cKO mice.	(Stempel et al., 2016)
	VTA	DA neurons	JWH-133 (10-20 mg/kg IP)	∩ AP and burst firing rate (dose-dep)	Blocked by AM630 (10 mg/kg). No effect in KO mice (Zimmer strain)	(Zhang et al., 2014)
Healthy (Rat)	Spinal cord	Wide dynamic range neurons	AM1241 (0.3 mg/kg, IV)	= spontaneous firing, ∩∩ C-fiber-mediated activity (total suppression)	Blocked by SR144528 (1 mg/kg, IV)	(Nackley et al., 2004)
Spinal nerve ligation (Rat)	Thalamus	Ventral posterior nucleus neurons	JWH-133 (192 µM, 2 weeks post induction, local pressure ejection. Effect 30 min post admin)	∩ Spontaneous activity, ∩ mechanically evoked responses	Blocked with SR144528 (48 ng)	(Jhaveri et al., 2008)
Carrageenan induced inflammation (Rat)	Spinal cord	Wide dynamic range neurons	AM1241 (0.3 mg/kg, IV, just before insult)	= spontaneous firing, ∩ C-fiber-mediated activity	Blocked by SR144528 (1 mg/kg, IV)	(Nackley et al., 2004)
	Spinal cord	Wide dynamic range neurons	AM1241 (0.3 mg/kg, local : intraplantar)	∩ spontaneous firing	Blocked by SR144528 (1 mg/kg, IV)	(Nackley et al., 2004)
	Spinal cord	Wide dynamic range dorsal horn neurons	JWH-133 (10µg/50µL, intraplantar, 10 min before recording)	∩ mechanically evoked responses	Blocked by SR144528 (10 µg/50µL)	(Elmes et al., 2004)
	Spinal cord	Dorsal horn neurons	Anandamide (50µg/50µL, intraplantar, 10 min before recording)	∩ mechanically evoked responses	Blocked by SR144528 (10 µg/50µL)	(Sokal et al., 2003)
Spinal nerve ligation (Rat)	Spinal Cord	Deep convergent dorsal horn neurons	JWH-133 (8-486 ng/50 µL, local spinal administration)	∩ mechanically evoked responses	Blocked by SR144528 (0.001 µg/50 µL, local)	(Sagar et al., 2005)
	Spinal Cord	Wide dynamic range dorsal horn neurons	JWH-133 (5-15µg/50µL, intraplantar, 10 min before recording)	∩ mechanically evoked responses, ∩ noxious-evoked responses	Attenuated by SR144528 (10 µg/50µL)	(Elmes et al., 2004)

SYNAPTIC TRANSMISSION						
Alzheimer's Disease (APP/PS1, Mouse)	Hippo-campus	CA1 Neurons	MDA7 (14 mg/kg, IP, ½ day, from 3- to 8-month-old)	↗ LTP	-	(Wu et al., 2017)
Alzheimer's Disease (intracerebral Aβ ₁₋₄₁ , Rat)	Hippo-campus	CA1 Neurons	MDA7 (1.5-15 mg/kg, IP, daily for 14 days)	↗ LTP, ↗ eEPSC amplitude	-	(Wu et al., 2013)

Abbreviations : 5-HT, 5-hydroxytryptamine receptor ; Aβ, amyloid β ; AP, action potential ; APP, amyloid precursor protein ; CA1 and 3, Cornu ammonis 1 and 3 ; DA, dopamine ; dose-dep, dose-dependent ; eEPSC, evoked excitatory post-synaptic current ; IN, intranasal ; IP, intra-peritoneal ; KO, knock-out ; LTP, long term potentiation ; MCAO, middle cerebral artery occlusion ; NAc, nucleus accumbens ; PS1, presenilin 1 ; Ref, reference ; VTA, ventral tegmental area.

Supplementary Table 6. Feeding. Behavioral outcome following CB2R activation or blockade is either enhanced (↗), decreased (↘) or unchanged (=). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), or the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION				
<i>Pharmacological activation</i>				
Healthy (Mouse)	JWH-015 (10 mg/kg, IP)	↘ food intake	Blocked by AM630 (5 mg/kg, IP)	(Verty et al., 2015)
	JWH-133 (10 mg/kg, IP, 1/day during CPP development, for 8 days)	= food intake	-	(Martín-Sánchez et al., 2019)
Diet-induced obesity (Mouse)	JWH-015 (10 mg/kg, IP, daily for 21 days)	↘ food intake (first 6 days) ↘ body weight (entire treatment duration), ↘ feed efficiency ratio	-	(Verty et al., 2015)
High fat diet (Rat)	β-caryophyllene (30 mg/kg, PO, daily for 4 weeks)	= weight gain. ↘ visceral fat index	Blocked by AM630 (1 mg/kg, IP)	(Youssef et al., 2019)
Parkinson's disease (MPTP, mouse)	AM1241 (0.75-12 mg/kg, IP, daily for 12 days starting 24 h after the last injection of MPTP)	Prevention of MPTP-induced weight loss	-	(Shi et al., 2017)
<i>Genetic overexpression</i>				
CB2xP	-	= basal food intake. ↘ fasting-induced intake after 120 min. ↘ body weight (after 18-week-old, but not at 12)	-	(Romero-Zerbo et al., 2012)
CB2R BLOCKADE				
<i>Pharmacological blockade</i>				
Healthy (Mouse)	AM630 (10 mg/kg, IP, 24h before test)	↘ food intake	-	(Ishiguro et al., 2010)
	AM630 (10 mg/kg, IP, 1h before test)	= food intake	-	(Martín-Sánchez et al., 2019)
Healthy (Rat)	SR144528 (0.1-1 mg/kg, IP, 45 min before test)	↘ food intake	-	(Adamczyk et al., 2012)
12h food deprivation (Mouse)	AM630 (10 mg/kg, IP, 24h before test)	↗ food intake	-	(Ishiguro et al., 2010)
<i>Genetic inactivation</i>				
Healthy, CB2R KO (Zimmer strain)	-	↗ food intake	-	(Agudo et al., 2010)
Healthy, CB2R KO (Deltagen strain)	-	↗ visceral fat mass	-	(Schmitz et al., 2016)

Abbreviations : CB2xP, mice overexpressing CB2R ; CPP, conditioned place preference ; IP, intra-peritoneal ; KO, knock-out ; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ; PO, per os ; Ref, reference.

Supplementary Table 7. Motor function. Behavioral outcome following CB2R activation or blockade is either enhanced (\nearrow), decreased (\searrow) or unchanged ($=$). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{um1Dgen}/J*, #005786), the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000), or the “Romero strain” generated with the cre-lox method (López et al., 2018)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
Pharmacological activation					
Healthy (Mouse)	JWH-133 (20 mg/kg, IP)	Locomotor activity boxes, Ring test	\searrow locomotor activity, catalepsy	-	(Liu et al., 2017)
	β -caryophyllene (100 mg/kg, IP)	Open field, rotarod, forced swim test	= locomotor activity	-	(Oliveira et al., 2016)
	JWH-015 (1-20 mg/kg, IP, 10 min pre-test)	Activity monitoring	\searrow general locomotor activity (dose dep), \searrow stereotype behavior	-	(Onaivi et al., 2008)
	JWH-133 (10-20 mg/kg, IP)	Open field	\searrow basal and cocaine-enhanced locomotion (dose dep)	Blocked by AM630 (10 mg/kg, IP). No effect in KO mice (Zimmer strain)	(Xi et al., 2011)
	HU-910 (30 mg/kg, IP, 30 pre-test)	Elevated Open Field	\searrow Locomotion (total distance)	-	(Cortez et al., 2022)
Healthy (Rat)	GW833972A (100 nM, intranigral microinjection)	Observation chamber	Induction of contralateral turning (2-4 turns/min)	Blocked by AM630 (50 nM)	(Sánchez-Zavaleta et al., 2018)
	JWH-133 (20 mg/kg, IP, 30 min pre-test)	Open Field	\searrow Locomotion (total distance)	Attenuated by AM630 (3 mg/kg, IP)	(Spiller et al., 2019)
	GW405833 (100 mg/kg, IP, 1 to 5h pre-test)	Rotarod, catalepsy assay	\searrow motor performances + cataleptic effect + ataxia	No effect at 30 mg/kg	(Valenzano et al., 2005)
Amyotrophic lateral sclerosis (Mouse)	HU-308 (5mg/kg, IP, daily from 65 to 90 days old)	Rotarod	\nearrow locomotor activity	-	(Espejo-Porras et al., 2019)
Amphetamine-induced hyperlocomotion (Mouse)	HU-910 (3-60 mg/kg, IP, 60 min pre-injury, 70 min pre-test)	Elevated open field	No effect on hyperlocomotion	-	(Cortez et al., 2022)
Chronic Mild Stress (Mouse)	JWH-015 (1-20 mg/kg, IP, 10 min pre-test)	Activity monitoring (stereotypic counts like rearing behavior and other repetitive behaviors)	\searrow stereotype behavior	-	(Onaivi, 2006)
High fat diet (Rat)	β -caryophyllene (30 mg/kg, PO, daily for 4 weeks)	Open field	\nearrow spontaneous locomotor activity and exploratory behavior	Blocked by AM630 (1 mg/kg, IP)	(Youssef et al., 2019)
Intracerebral hemorrhage (Rat)	JWH-133 (1.5 mg/kg, IP, 1h post-injury)	Modified Neurological Severity Score, forelimb placing test, corner turn test	\nearrow sensorymotor and balance function	Blocked by SR144528 (3 mg/kg IP, 3 min before agonist)	(Li et al., 2018)
	JWH-133 (1.5 mg/kg, IP, 1h post-injury)	Modified Neurological Severity Score	\nearrow sensorymotor and balance function	Blocked by SR144528 (3 mg/kg IP, 3 min before agonist)	(Li et al., 2018)
LPS-induced sickness behavior (Mouse)	1-phenylisatin (20 mg/kg, PO, once daily for 7 days)	Open Field	\nearrow locomotor activity	LPS 1.5 mg/kg IP, 7th day of treatment	(Sahu et al., 2019)
MK801-induced hyperlocomotion (Mouse)	HU-910 (0.3-30 mg/kg, IP, 10 min pre-injury, 30 min pre-test)	Elevated open field	\searrow hyperlocomotion	Blocked by AM630 (1 mg/kg, IP)	(Cortez et al., 2022)
Seizure (PTZ, Mouse)	β -caryophyllene (30-300 mg/kg, IP)	Rotarod	= locomotor activity	-	(Tchekalarova et al., 2018)
Spinal cord injury (Mouse)	O-1966 (5 mg/kg, IP, 2 injections, 1h and 24h post-injury)	Open Field (Basso Mouse Scale (BMS), Basso Beattie-Bresnahan (BBB) locomotorscale)	\nearrow motor function	-	(Adhikary et al., 2011)
Spinal cord injury (Rat)	JWH-015 (3 mg/kg, IP, daily for 7 days post-injury)	Beam walking test, catwalk,	\nearrow functional recovery	-	(Latini et al., 2014)
Stroke (MCAO, Rat)	AM1241 (2.5 mg/kg, IP, 5 min pre- injury. Test 2 days later)	Elevated bodyswing test, Bederson's score (postural reflex test)	\nearrow functional recovery	-	(Yu et al., 2015)
Surgery-induced cognitive impairment (Mouse)	JWH-133 (2 mg/kg, IP, immediately after recovery from anesthesia, and repeated 24h post-injury)	Open Field	= locomotor activity	-	(Sun et al., 2017)
Traumatic brain injury (CCI, Mouse)	GP1a (3 mg/kg, IP, 10 min post-injury)	Stationary beam walk and accelerating rotarod task	\nearrow motor coordination	-	(Braun et al., 2018)
	O-1966 (5 mg/kg, IP, 1h and 24h post-injury)	Rotarod, glass cylinder test	\nearrow locomotor performance. \nearrow usage of forelimb	-	(Elliott et al., 2011)
Traumatic brain injury (CHI, Mouse)	HU910 (10 mg/kg, IP, 1h post-injury)	Neurological severity score (evaluation of walk, balance, startle reflex, seeking behavior)	\nearrow locomotor performance	Blocked by SR144528 and AM630 (1 mg/kg, IP)	(Magid et al., 2019)
Parkinson's disease (MPTP, Mouse)	AM1241 (0.75-12 mg/kg, IP, daily for 12 days, 24h post-injury)	Rotarod, pole test (day 5 post MPTP)	\nearrow motor function	-	(Shi et al., 2017)
	β -caryophyllene (10 mg/kg, IP, daily for 5 days, 24h pre-injury)	Pole test, gait lab, beam test	\searrow MPTP-induced movement impairment, \searrow stride length impairment, \searrow balance impairment	Blocked by AM630 (3 mg/kg, IP), no effect in control mice	(Viveros-Paredes et al., 2017)

	AM1241 (6 mg/kg, IP, 5 days post-injury, for 2 weeks)	Pole test	↗ motor function	No effect in KO mice (strain ?)	(He et al., 2020)
Parkinson's disease (6-OHDA, Mouse)	GW842166x (1 mg/kg, IP, daily for 3 weeks, post-injury)	Pole test, balance beam, grip strength, rotarod	↗ motor function	Blocked by AM630 (10 mg/kg, IP)	(Yu et al., 2021)
Parkinson's disease (LRRK2 transgenic mouse)	HU-308 (5 mg/kg, IP, daily, 12 to 18 months of age)	Rotarod, hanging wire test, pole test	↗ motor function (for hanging wire test only)	Blocked by SR144528 (1 mg/kg, IP)	(Palomogaro et al., 2016)
Genetic overexpression					
CB2xP mouse	-	Open field	= basal motor activity	-	(Aracil-Fernández et al., 2012)
Cell-specific inducible overexpression (Camk2a-Cre, Gad2-Cre, Cx3cr1-Cre)	-	Open field	= basal motor activity	-	(Li and Kim, 2017)
CB2R BLOCKADE					
Pharmacological blockade					
Healthy (Rat)	SR144528 (0.1-1 mg/kg, IP)	Optomo-Varimex cages (horizontal activity + distance moved in cm)	= basal locomotor activity	-	(Adamczyk et al., 2012)
Healthy (Mouse)	AM630 (3 mg/kg, IP)	Open field	= motor activity	-	(Li and Kim, 2016b)
	AM630 (10 mg/kg, IP, 1h pre-test)	IR motor activity monitor	= spontaneous locomotor activity	-	(Martín-Sánchez et al., 2019)
	SR144528 (1 mg/kg, IP)	Activity monitor	↗ General locomotor activity	-	(Onaivi et al., 2008)
	AM630 (3 mg/kg, IP)	Pole test, gait lab, beam test	= locomotor activity, = stride length, = balance	-	(Viveros-Paredes et al., 2017)
Stroke (MCAO, Mouse)	SR144528 (5 mg/kg, IP, 2 days post-injury)	Staircase pellet-reaching test, open field	↘ spontaneous motor recovery	-	(Bravo-Ferrer et al., 2017)
Surgery-induced cognitive impairment (Mouse)	AM630 (3mg/kg, IP, immediately after recovery from anesthesia, and repeated 24h post-injury)	Open Field	= motor activity	-	(Sun et al., 2017)
Traumatic Brain Injury (Mouse, air blast injury)	SMM-189 (6 mg/kg, IP, 2h post-injury and daily for 14 days)	Rotarod, open field	↗ locomotor activity	-	(Reiner et al., 2014)
Genetic invalidation					
CB2R KO (Zimmer strain)	-	Open field	↘ spontaneous locomotor activity	-	(Ortega-Alvaro et al., 2011)
Amyotrophic Lateral Sclerosis /CB2R KO (Romero strain)	-	Rotarod	↘ motor function	-	(Rodríguez-Cueto et al., 2021)
Cell-specific inducible deletion (Camk2a-Cas9, Gad2-Cas9, Cx3cr1-Ca9)	-	Open field	= basal motor activity	-	(Li and Kim, 2017)
DAT-CB2R cKO Mouse	-	IR photobeam-controlled open-field	↗ basal motor activity	-	(Canseco-Alba et al., 2019)
	-	Open field and wheel running tests	↗ motor activity (distance moved + rearing)	-	(Liu et al., 2017)
Huntington's disease (R6/2) CB2R KO (Zimmer strain)	-	Rotarod	↘ motor function	-	(Palazuelos et al., 2009)

Abbreviations : 6-OHDA, 6-hydroxydopamine ; Camk2a, Calcium/Calmodulin Dependent Protein Kinase II Alpha ; CB2xP, mice overexpression CB2R ; CCI, Controlled cortical impact ; CHI, closed-head injury ; cKO, conditional knock-out ; Cre, Cre recombinase ; CX3CR1, CX3C motif chemokine receptor 1 ; DAT, dopamine active transporter ; dose-dep, dose-dependent ; Gad2, glutamate decarboxylase 2 ; IP, intra-peritoneal ; KO, knock-out ; LPS, lipopolysaccharide ; LRRK2, leucine-rich repeat kinase 2 ; MCAO, middle cerebral artery occlusion ; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ; PO, per os ; PTZ, Pentylentetrazol ; Ref, reference ; TBI, traumatic brain injury.

Supplementary Table 8. Learning and memory. Behavioral outcome following CB2R activation or blockade is either enhanced (\nearrow), decreased (\searrow) or unchanged ($=$). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{um1Dgen}/J*, #005786), or the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
Pharmacological activation					
Healthy (Mouse)	β -caryophyllene (100 mg/kg, IP)	NOR	\nearrow recognition index	-	(Oliveira et al., 2016)
	β -caryophyllene (10-50 mg/kg, IP)	MWM	\nearrow Spatial learning (dose dep)	-	(Tchekalarova et al., 2018)
	JWH-133 (0.5-2 mg/kg, IP)	Step down inhibitory avoidance test	\nearrow aversive memory performance	No effect in KO mice (Zimmer strain)	(García-Gutiérrez et al., 2013)
	JWH-133 (0.25-1 mg/kg, IP)	Passive avoidance test	= acquisition, \nearrow consolidation of long-term memory	-	(Kruk-Slomka et al., 2022)
	JWH-133 (2 mg/kg, IP)	Passive avoidance test	\nearrow acquisition and consolidation of memory	-	(Kruk-Slomka et al., 2016)
	GP1a (1-100 μ g, intra-CA1, post-training)	Passive avoidance test	\searrow memory consolidation	-	(Nasehi et al., 2018)
Healthy (Rat)	GP1a (150 ng, Intra-CA1 microinjection)	Step-through task	\searrow memory consolidation	-	(Nasehi et al., 2017)
Alzheimer's disease (Aβ1-42 + D-Gal, Mouse)	1-Phenylisatin (10-20 mg/kg, 31 days after first injection of A β 1-42+D-Gal)	MWM, Attentional set shifting test	\nearrow memory performance (MWM: acquisition + retrieval. ASST: reversal learning)	-	(Jayant et al., 2016)
Alzheimer's disease (APP/PS1, Mouse)	JWH-133 (0.2 mg/kg, IP, daily for 5 weeks at 3 months old (pre-symptomatic phase))	Two-object recognition test, active avoidance test	\nearrow memory performance (\nearrow recognition index)	-	(Aso et al., 2013)
	JWH-133 (0.2 mg/kg, IP, daily for 5 weeks at 6 months old (early-symptomatic phase))	Two-object recognition test, active avoidance test	\nearrow memory performance (\nearrow recognition index)	-	(Aso et al., 2013)
	JWH-015 (0.5 mg/kg, IP, daily for 8 weeks, start at 8-month-old)	NOR, MWM	\nearrow NOR memory. No effect on MWM performance	-	(Li et al., 2019)
	MDA7 (14 mg/kg, IP, 1/2 day, from 3- to 8-month-old)	MWM	\nearrow memory performance	-	(Wu et al., 2017)
Alzheimer's disease (STZ, Mouse)	1-Phenylisatin (10-20 mg/kg, PO, once daily for 30 days, 4 days after first injection of STZ)	MWM : D16-19. Attentional set shifting test: testing session on D30	\nearrow memory performance (MWM : acquisition + retrieval. ASST : reversal learning)	-	(Jayant et al., 2016)
Alzheimer's disease (Tg APP 2576, Mouse)	JWH-133 (0.2 mg/kg, PO, 1/day in the drinking water for 4 months, start at 7 months (before A β deposition))	NOR	\nearrow recognition memory	-	(Martín-Moreno et al., 2012)
Alzheimer's disease (intrahippocampal Aβ1-42, Rat)	WIN55,212 (10 μ g, intra hippocampal, 1h post A β 1-42 and repeated day 3, 5 and 7)	MWM	\nearrow Spatial learning	Partially blocked by SR144528 (70 μ g, intra-hippocampal)	(Fakhfouri et al., 2012)
Alzheimer's disease (intracerebral Aβ1-41, Rat)	MDA7 (1.5-15 mg/kg, IP, daily for 14 days)	MWM	\nearrow Spatial learning (dose dep)	Blocked by AM630 (5 mg/kg, IP)	(Wu et al., 2013)
Age-related cognitive decline (Mouse)	β -caryophyllene (100-300 mg/kg, IP, 3/week for 1 week)	Y-maze	\nearrow memory performance	-	(Lindsey et al., 2019)
D-AP5-induced memory impairment (Rat)	GP1a (50 ng, Intra-CA1 microinjection, post training)	Step-through task	\nearrow memory consolidation	-	(Nasehi et al., 2017)
High fat diet (Rat)	β -caryophyllene (30 mg/kg, PO, daily for 4 weeks)	Y maze	\nearrow memory performance	Blocked by AM630 (1 mg/kg, IP)	(Youssef et al., 2019)
HIV-1 glycoprotein 120 induced neural injury (Rat)	Win55,212-2 (3 mg/kg/d, IP, for 3 days before injury)	MWM	\nearrow learning and memory performance	Blocked by AM630 (1.5 mg/kg/d, IP)	(Wang et al., 2022)
MK-801-induced cognitive impairment (Schizophrenia, Mouse)	HU-910 (3-30 mg/kg, IP, once a day, for 7 days, 24h after the end of MK-801 administration)	NOR	\nearrow memory performance	-	(Cortez et al., 2022)
Okadaic acid-induced neurodegeneration (Rat)	JWH-133 (0.2 mg/kg, IP, for 13 days)	MWM	\nearrow spatial memory performance	-	(Çakır et al., 2019)
Sepsis-induced encephalopathy (Mouse)	HU-308 (2.5 mg/kg, IP, 30 post injury and 1/day for 3 days)	NOR, MWM	\nearrow recognition and spatial memory	-	(Yang et al., 2022)
Surgery-induced cognitive impairment (Mouse)	JWH-133 (2 mg/kg, IP, immediately after recovery from anesthesia, and repeated 24h post-injury)	Fear conditioning (context and cue)	\nearrow contextual fear (hippocampal-dep) memory. = tone fear (hippocampal-indep) memory	-	(Sun et al., 2017)
Stroke (Mouse)	O-1966 (5 mg/kg, IP, 1h prior to and 2- and 5-days post injury)	NOR, food motivated operant procedure	\nearrow memory performance	-	(Ronca et al., 2015)
Vascular dementia (Rat)	Paeoniflorin (40 mg/kg, IP, daily for 28 days one week post injury)	MWM	\nearrow spatial memory	Blocked by AM630 (3 mg/kg, IP)	(Luo et al., 2018)
	HU-308 (3 mg/kg, IP, daily for 28 days one week post injury)	MWM	\nearrow spatial memory	-	(Luo et al., 2018)

	β-caryophyllene (30-144 mg/kg, IP, administered as a HPβCD/BCP complex, 1/day for 4 weeks, starting 4 weeks post injury)	MWM	↗ spatial memory	-	(Lou et al., 2017)	
Genetic overexpression						
	Cell-specific inducible overexpression (Camk2a-Cre, Gad2-Cre)	-	Fear memory test, Y-maze, NOR	= cued and contextual fear response. = novelty memory, = spatial working memory	-	(Li and Kim, 2017)
	Microglia-specific inducible overexpression (Cx3cr1-Cre)	-	Fear memory test, Y-maze, NOR	= cued fear memory. ↗ contextual fear memory. = novelty memory, = spatial working memory	-	(Li and Kim, 2017)
CB2R BLOCKADE						
Pharmacological blockade						
Healthy (Mouse)	AM630 (1-3 mg/kg, IP, immediately after foot shock (pretraining session))	Step down inhibitory avoidance test	↘ short (1h) and long (24h) term aversive memory	No effect in KO mice (Zimmer strain)	(García-Gutiérrez et al., 2013)	
	AM630 (3 mg/kg, IP)	Cued fear conditioning (tone), Contextual fear conditioning	= cued and contextual fear memory, = spatial working memory.	-	(Li and Kim, 2016b)	
	AM630 (0.5-3 mg/kg, IP, 30 min before the first trial or post training)	Passive avoidance test	↗ acquisition and consolidation of long-term memory	-	(Kruk-Slomka et al., 2016)	
	AM630 (0.25-1 mg/kg, IP, 30 min before the first trial and 24h after)	Passive avoidance test	↗ acquisition and consolidation of long-term memory	-	(Kruk-Slomka et al., 2022)	
Healthy (Rat)	AM630 (50-100 ng, Intra-CA1 microinjection, post-training)	Step-through task	↘ memory consolidation	-	(Nasehi et al., 2017)	
Surgery-induced cognitive impairment (Mouse)	AM630 (3mg/kg, IP, immediately after recovery from anesthesia, and repeated 24h post-injury)	Fear conditioning (sound + electrical footshock or context)	↘ contextual fear memory. = tone fear memory	-	(Sun et al., 2017)	
D-AP5-induced memory impairment (Rat)	AM630 (50 ng, Intra-CA1 microinjection, post-training)	Step-through task, Isobologram analysis	↗ memory consolidation (D-AP5>0.5µg) or ↘ (D-AP5<0.5µg)	Synergic effect between, D-AP5 and AM630	(Nasehi et al., 2017)	
Vascular dementia (Rat)	AM630 (3 mg/kg, IP, daily for 28 days one-week post-injury)	MWM	↘ spatial memory	-	(Luo et al., 2018)	
Genetic deletion						
Healthy, CB2R KO (Zimmer strain)	-	Step down inhibitory avoidance test	↘ short (1h) and long (24h) term aversive memory	-	(García-Gutiérrez et al., 2013)	
	-	Step down inhibitory avoidance	↘ short (1-3h) and long (24h) term memory	-	(Ortega-Alvaro et al., 2011)	
	-	MWM	↗ spatial memory at 6 months (no difference at 9 and 14 months)	-	(Schmöle et al., 2015)	
	-	MWM, Contextual fear conditioning	↘ spatial learning and memory, ↘ hippocampus-dependent contextual memory	-	(L. Wang et al., 2018)	
Healthy, CB2R KO (Deltagen strain)	-	Cued fear conditioning, Contextual fear conditioning, Y-maze	↘ contextual fear memory (but not cued). ↗ spatial working memory.	-	(Li and Kim, 2016b)	
	-	NOR	= recognition memory	-	(Galán-Ganga et al., 2021)	
Pyramidal cells-specific inducible deletion (Camk2a-Cas9)	-	Fear memory test, Y-maze, NOR	= cued and contextual fear response, = novelty memory. ↗ spatial working memory	-	(Li and Kim, 2017)	
Interneuron-specific inducible deletion (Gad2-Cas9)	-	Fear memory test, Y-maze, NOR	= cued and contextual fear response. = novelty memory, = spatial working memory	-	(Li and Kim, 2017)	
Microglia-specific inducible deletion (Cx3cr1-Cas9)	-	Fear memory test, Y-maze, NOR	= cued fear memory. ↘ contextual fear memory. ↗ novelty memory. = spatial working memory	-	(Li and Kim, 2017)	
Alzheimer's disease APP/PS1*CB2R KO (Zimmer strain)	-	MWM	↗ spatial memory at 6 months (No difference at 9 and 14 months)	-	(Schmöle et al., 2015)	
	9 and 14 months	MWM	↗ spatial memory	-	(Schmöle et al., 2018)	
Aging, CB2KO (Zimmer strain)	3, 12 and 18 months	Partner recognition, MWM	↘ social memory. = spatial learning and memory	-	(Komorowska-Müller et al., 2021b)	
Isoflurane-induced spatial cognitive impairment, CB2R KO (Deltagen strain)	-	MWM	↘ spatial learning and memory	-	(Li et al., 2021)	
Tau induced neurodegeneration, CB2R KO (Deltagen strain)	-	NOR	↗ recognition memory	-	(Galán-Ganga et al., 2021)	

Abbreviations : Aβ, amyloid β ; APP, amyloid protein precursor ; ASST, attentional set shifting test ; CA1, Cornu ammonis 1 ; Camk2a, Calcium/Calmodulin Dependent Protein Kinase II Alpha ; Cre, cre recombinase ; CX3CR1, CX3C motif chemokine receptor 1 ; D-AP5, D-2-amino-5-phosphonopentanoate ; D-Gal, D-galactose ; Gad2, glutamate decarboxylase 2 ; HIV, human immunodeficiency virus ; IP, intra-peritoneal ; KO, knock-out ; MWM, Morris water maze ; NOR, novel object recognition test ; Physio, physiological state ; PO, per os ; PS1, presenilin 1 ; Ref, reference ; STZ, streptozotocin.

Supplementary Table 9. Mood disorder. Behavioral outcome following CB2R activation or blockade is either enhanced (↗) or decreased (↘) or unchanged (=). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), or the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
<i>Pharmacological activation</i>					
Healthy (Mouse)	JWH-015 (1-20 mg/kg, IP, daily)	Sucrose consumption	↘ depression	-	(Onaivi et al., 2008)
	JWH-015 (1-20 mg/kg, IP)	Light/dark box	↗ anxiety	-	(Onaivi et al., 2008)
	JWH-015 (10 mg/kg, IP, daily for 21 days)	Forced swim test, elevated plus maze	= depressive-like behavior. ↘ anxiety	-	(Verty et al., 2015)
	JWH-133 (0.5-2 mg/kg, IP, twice a day for 7 days)	Light/dark box, elevated plus maze	↗ anxiety	-	(García-Gutiérrez et al., 2012)
Healthy (Rat)	GW405833 (30 mg/kg, IP)	Marble-burying behavior test	= anxiety	-	(Valenzano et al., 2005)
Anxiety (S1 mouse)	JWH-133 (IP, 5 mg.kg)	Elevated Plus Maze	= anxiety	-	(Ten-Blanco et al., 2022b)
Chronic Mild Stress (Mouse)	JWH-015 (1-20 mg/kg, IP, daily)	Sucrose consumption, light/dark box	= CMS-induced anxiety and anhedonia	-	(Onaivi et al., 2008)
Chronic restraint stress (Rat)	β-caryophyllene (25-100 mg/kg, IP, daily for 28 days)	Tail suspension test, forced swim test,	↘ depression	-	(Hwang et al., 2020)
High fat diet (Rat)	β-caryophyllene (30 mg/kg, PO, daily for 4 weeks)	Open-field, elevated plus maze, and light/dark box, forced-swim test	↘ high fat diet-induced anxiety and depression	Blocked by AM630 (1 mg/kg, IP)	(Youssef et al., 2019)
LPS-induced sickness behavior (Mouse)	1-phenylisatin (20 mg/kg, PO, once daily for 7-days)	Open field test, forced swim test, tail suspension test	↘ anxiety, depression	-	(Sahu et al., 2019)
Sepsis-induced encephalopathy (Mouse)	HU-308 (2.5 mg/kg, IP, 30 post injury and 1/day for 3 days)	Open field	↘ anxiety	-	(Yang et al., 2022)
Neuropathic pain (PSN, Mouse)	JWH-133 (0.3 mg/kg/inf, IV self administration)	Elevated-plus maze	↘ anxiety	-	(Cabañero et al., 2020)
Traumatic brain injury (Mouse)	GP1a (3 mg/kg, IP, 10 min post injury)	Open field	↘ anxiety	-	(Braun et al., 2018)
<i>Genetic overexpression</i>					
Healthy, CB2xP	-	Open field, light-dark box, elevated plus maze	↘ anxiety	-	(García-Gutiérrez and Manzanares, 2011)
	-	Tail suspension test, novelty-suppressed feeding test, unpredictable chronic mild stress tests, Forced swimming test, sucrose intake	↘ acute and chronic depression	-	(García-Gutiérrez et al., 2010)
	-	Light/dark box, open field, elevated plus maze, tail suspension test, novelty suppressed feeding, chronic mild stress, sucrose consumption	↘ depression and anxiogenic-like behavior	-	(Romero-Zerbo et al., 2012)
Cell-specific inducible overexpression (Cx3cr1-Cre, Gad2-Cre)	-	Elevated O-maze, tail suspension test, Open field	=anxiety, depression	-	(Li and Kim, 2017)
Cell-specific inducible overexpression (Camk2a-Cre)	-	Elevated O-maze, tail suspension test, Open field	↘ anxiety (open field only), = depression	-	(Li and Kim, 2017)
CB2R BLOCKADE					
<i>Pharmacological blockade</i>					
Healthy (Mouse)	AM630 (1-3 mg/kg, IP, 30 min before test for acute, twice a day for 7 days for chronic)	Light/dark box, elevated plus maze	↘ anxiety (for both acute and chronic treatment)	Blocked by JWH-133 (2 mg/kg, IP)	(García-Gutiérrez and Manzanares, 2011)
	AM630 (1-3 mg/kg, IP, 30 min before test for acute, twice a day for 4 weeks for chronic)	Forced swimming test (acute stress), Unpredictable chronic mild stress tests (chronic stress)	↘ depression (acute and chronic)	No effect in CB2xP mice	(García-Gutiérrez et al., 2010)
	AM630 (3 mg/kg, IP)	Elevated O-Maze, open field	= anxiety	-	(Li and Kim, 2016b)
	AM630 (1 mg/kg, IP, daily)	Sucrose consumption	= depression	-	(Onaivi et al., 2008)
Anxiety (DBA/2 Mouse)	AM630 (IP, twice a day for 7 days (chronic). Test 15h after the last injection)	Light/dark box	↘ anxiety	-	(García-Gutiérrez and Manzanares, 2011)
Anxiety (S1 mouse)	SR144528 (3 mg/kg, IP)	Elevated Plus Maze	↘ anxiety	-	(Ten-Blanco et al., 2022b)
Orexin-induced fear extinction deficit (mouse)	AM630 (3 mg/kg, IP, immediately after the extinction session)	Fear extinction	↗ fear extinction	-	(Ten-Blanco et al., 2022a)
Traumatic Brain Injury (Mouse, air blast injury)	SMM-189 (6 mg/kg, IP, 2h post-injury and daily for 14 days)	Tail suspension test, fear extinction	↘ depression, ↗ fear extinction, ↘ fear	-	(Reiner et al., 2014)
<i>Genetic deletion</i>					
CB2R KO (Deltagen strain)	-	Elevated O-Maze, open field	= anxiety	-	(Li and Kim, 2016b)
CB2R KO (Zimmer strain)	-	Light-dark box test, Elevated +-maze, Tail suspension test	↗ anxiety, ↗ despair behavior	-	(Ortega-Alvaro et al., 2011)

Cell-specific inducible deletion (Camk2a-Cas9, Gad2-Cas9, Cx3cr1-Cas9)	-	Elevated 0-maze, tail suspension test, Open field	= anxiety, depression	-	(Li and Kim, 2017)
DAT-CB2R cKO	-	Forced swim and tail-suspension test, black and white box, elevated plus-maze tests	↗ depression	-	(Liu et al., 2017)
Aging, CB2R KO (Zimmer strain)	3, 12 and 18 months	0-maze	↘ anxiety	-	(Komorowska-Müller et al., 2021b)
Chronic Mild Stress, DAT-CB2R cKO	-	Sucrose intake	↘ stress-induced anhedonia	-	(Liu et al., 2017)

Abbreviations : Camk2a, Calcium/Calmodulin Dependent Protein Kinase II Alpha ; CB2xP, mice overexpression CB2R ; cKO, conditional knock-out ; CMS, chronic mild stress ; Cre, Cre recombinase ; CX3CR1, CX3C motif chemokine receptor 1 ; DAT, dopamine active transporter ; Gad2, glutamate decarboxylase 2 ; IP, intra-peritoneal ; IV, intra-venous ; KO, knock-out ; LPS, lipopolysaccharide ; PO, per os ; PSN, partial sciatic nerve ligation model ; Ref, reference.

Supplementary Table 10. Reward and addiction. Behavioral outcome following CB2R activation or blockade is either enhanced (↗), decreased (↘) or unchanged (=). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the "Deltagen strain", with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{um1Dgen}/J*, #005786), or the "Zimmer strain" with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
Pharmacological activation					
Alcohol (Mouse)	β-caryophyllene (25-100 mg/kg, IP, daily)	Two-bottle choice, EtOH conditioning	↘ EtOH consumption and preference. ↘ EtOH elicited conditioning	Blocked by AM630 (3 mg/kg, IP)	(Al Mansouri et al., 2014)
	JWH-133 (10 mg/kg, IP, 1/D during CPP development, 1h before conditioning session (8 days))	Conditioned place preference	↘ EtOH-induced CPP	EtOH: 10%, 12.6 mL/kg, IP	(Martin-Sánchez et al., 2019)
	JWH-133 (10-20 mg/kg, IP 30 minutes before behavioral testing)	Conditioned place preference	= EtOH intake, = EtOH-induced CPP expression	EtOH: 20%, 2g/kg, IP	(Powers et al., 2015)
Alcohol, Chronic Mild Stress (Mouse)	JWH-015 (20 mg/kg, IP, chronic (daily))	EtOH consumption monitoring	↗ EtOH intake	No effect in non-stressed animals. EtOH: 4%, PO	(Ishiguro et al., 2007; Onaivi et al., 2008)
Cocaine (Mouse)	JWH-133 (3 mg/kg, IP, pre-treatment)	Conditioned place preference	↘ cocaine induced CPP	Cocaine: 7,5 mg/kg, IP	(Canseco-Alba et al., 2019)
	JWH-133 (1-10 mg/kg, IP, 30 min before cocaine)	Conditioned place preference	↘ cocaine induced-sensitization. ↘ cocaine-induced CPP	Cocaine: 20 mg/kg, IP	(Lopes et al., 2020)
	JWH-133 (10-20 mg/kg, IP; 1-1000 μM, intra NAc)	Cocaine self-administration	↘ cocaine self-administration (dose-dep), ↗ cocaine's rewarding efficacy.	Cocaine: 10mg/kg, IP. Blocked by AM630 (10 mg/kg, IP). No effect in KO mice (Zimmer strain)	(Xi et al., 2011)
	GW405833 (3-10 mg/kg, IP)	Cocaine self-administration	↘ cocaine self-administration (dose-dep)	Cocaine : 10, 20 mg/kg, IP	(Xi et al., 2011)
	JWH-133 (10-20 mg/kg, IP or 10-20 μg, intranasal, 30min before testing)	Cocaine self-administration	↘ cocaine self-administration	Cocaine: 0.5 mg/kg/injection, IV. No effect in KO mice (Zimmer strain)	(Zhang et al., 2015)
	JWH-133 (1-3 μg/side, Intra VTA microinjection, 30 min before testing)	Cocaine self-administration	↘ cocaine self-administration	Cocaine: 0.5 mg/kg/injection, IV. Blocked by AM630 (3μg/side). No effect in KO mice (Zimmer strain)	(Zhang et al., 2014)
Cocaine (Rat)	O-1966 (20 mg/kg, IP, 15 before cocaine)	Conditioned place preference	↘ cocaine induced CPP	-	(Ignatowska-Jankowska et al., 2013)
	JWH-133 (3-10 mg/kg, IP, pre-pairing administration)	Conditioned place preference	↘ cocaine induced CPP. ↘ cocaine-induced conditioned motor activity	Blocked by AM630 (5mg/kg, IP). Cocaine: 20 mg/kg, IP	(Delis et al., 2016)
	JWH-133 (10-20 mg/kg, IP, 30min before testing)	Cocaine self-administration	= cocaine self-administration	Cocaine: 0.5 mg/kg/injection, IV.	(Zhang et al., 2015)
Food (Mouse)	JWH-133 (25-50μg/side, intranasal)	Cocaine self-administration	25 μg : ↗ cocaine self-administration. 50 μg : ↘ cocaine self-administration	Cocaine: 0.5 mg/kg/injection, IV.	(Zhang et al., 2015)
	JWH-133 (10 mg/kg, IP, 1/day during CPP development, 1h before conditioning session (8 days))	Conditioned place preference	↘ food-induced CPP	-	(Martin-Sánchez et al., 2019)
Intracranial self-stimulation (Rat)	JWH-133 (20 mg/kg, IP, 30 min before test)	Brain stimulation reward (lateral hypothalamus)	↘ reward (↗ BSR threshold)	Attenuated by AM630 (3 mg/kg, IP)	(Spiller et al., 2019)
Morphine (Rat)	JWH-015 (1 mg/kg, IP)	Conditioned place preference	↘ Morphine-induced CPP	Morphine: 10 mg/kg, IP	(Grenald et al., 2017)
Nicotine (Mouse)	O-1966 (1-20 mg/kg, IP, 15 before nicotine)	Conditioned place preference	↗ CPP (dose dep)	Nicotine: 0,1 mg/kg, SC (=subthreshold dose)	(Ignatowska-Jankowska et al., 2013)

Sucrose (Mouse)	JWH-133 (1-3 µg/side, Intra VTA microinjection, 30 min before testing)	Sucrose self-administration	= sucrose self-administration	-	(Zhang et al., 2014)
	JWH-133 (10-20 mg/kg, IP 30 min before testing)	Sucrose self-administration	∖ sucrose self-administration	No effect in KO mice (Zimmer strain)	(Zhang et al., 2015)
Sucrose (Rat)	JWH-133 (10-20 mg/kg, IP 30 min before testing)	Sucrose self-administration	= sucrose self-administration	-	(Zhang et al., 2015)
Genetic overexpression					
Cocaine (CB2xP mouse)	-	Conditioned place preference	Conditioned place aversion. ∖ cocaine self-administration.	Cocaine: 20-40 mg/kg, IP	(Aracil-Fernández et al., 2012)
CB2R BLOCKADE					
Pharmacological blockade					
Alcohol (Mouse)	AM630 (3 mg/kg, IP, daily)	EtOH consumption monitoring	∖ Alcohol intake (not significant)	EtOH: 4%, PO	(Ishiguro et al., 2007)
	AM630 (10 mg/kg, IP, 1h before test session, post-conditioning)	Conditioned place preference (expression)	∖ Alcohol induced CPP (no effect at 5 mg/kg)	EtOH: 2 g/kg, IP	(Martín-Sánchez et al., 2019)
	AM630 (10 mg/kg, IP, 1/day during conditioning for 8 days)	Conditioned place preference (development)	= Alcohol induced CPP	EtOH: 2 g/kg, IP	(Martín-Sánchez et al., 2019)
	AM630 (10-20 mg/kg, IP)	Conditioned place preference	= Alcohol intake, = alcohol-induced CPP expression	EtOH: 2 g/kg, IP	(Powers et al., 2015)
Alcohol, Chronic Mild Stress (Mouse)	AM630 (3 mg/kg, IP, daily)	EtOH consumption monitoring	= Alcohol intake	EtOH: 4%, PO	(Ishiguro et al., 2007)
	AM630 (1 mg/kg, IP, daily)	EtOH consumption monitoring	∖ Alcohol intake	-	(Onaivi et al., 2008)
Cocaine (Mouse)	AM630 (3 µg/side, intra VTA microinjection)	Intravenous self-administration	= cocaine self-administration	-	(Zhang et al., 2014)
	SR144528 (0.1-1 mg/kg, IP, 45 min before test session)	Cocaine self-administration	∖ cocaine-induced reinstatement to drug seeking, = cocaine self-administration maintenance	-	(Adamczyk et al., 2012)
Cocaine (Rat)	AM630 (5 mg/kg, IP, pre-pairing)	Conditioned place preference	= Cocaine induced CPP. = Cocaine-induced conditioned motor activity	Cocaine: 20 mg/kg, IP	(Delis et al., 2016)
	AM630 (10 mg/kg, IP, 1h before test session, post-conditioning)	Conditioned place preference (expression)	= Food induced CPP	-	(Martín-Sánchez et al., 2019)
Nicotine (Mouse)	AM630 (3mg/kg, IP)	Conditioned place preference	∖ Nicotine-induced CPP (abolished). ∖ Nicotine self-administration	Nicotine: 0.5-25mg/kg/day, IV	(Navarrete et al., 2013)
	SR144528 (1-3 mg/kg, IP, 15 min before nicotine)	Conditioned place preference	∖ Nicotine-induced CPP (abolished at 3 mg/kg)	Nicotine: 0.5 mg/kg, SC	(Ignatowska-Jankowska et al., 2013)
Nicotine (Rat)	AM630 (5 mg/kg, IP, 30 min before the session)	Nicotine self-administration	= Nicotine self-administration	Nicotine: 30 µg/kg/infusion	(Gamaledin et al., 2012)
Genetic invalidation					
Alcohol, CB2R KO (Zimmer strain)	-	Conditioned place preference, two-bottle free choice assay	∕ Alcohol-induced CPP. ∕ Alcohol consumption	EtOH: 2 g/kg, PO	(Ortega-Álvaro et al., 2015)
	-	Conditioned place preference	∕ Alcohol-induced CPP	EtOH: 2 g/kg, IP	(Powers et al., 2015)
Alcohol, Cx3cr1-CB2R cKO	-	Conditioned place preference	= alcohol induced CPP	EtOH: 8%, PO	(Liu et al., 2020)
Alcohol, DATCnr2 cKO	-	Conditioned place preference	∖ alcohol induced CPP	EtOH: 8%, PO	(Liu et al., 2020)
Alcohol, Subacute stress, DAT-CB2R cKO	-	EtOH consumption monitoring	∖ alcohol consumption	-	(Liu et al., 2017)
Alcohol, Chronic Mild Stress, DAT-CB2R cKO	-	EtOH consumption monitoring	= alcohol consumption	-	(Liu et al., 2017)
Alcohol, cocaine, DAT-CB2R cKO	-	Conditioned place preference	∖ alcohol consumption. ∖ alcohol induced CPP. ∕ cocaine induced CPP	-	(Liu et al., 2017)
Cocaine, Amphetamine, Methamphetamine DAT-CB2R cKO	-	Conditioned place preference	∕ cocaine, amphetamine and methamphetamine-induced CPP	Cocaine: 7.5 mg/kg, IP, amphetamine: 5 mg/kg, IP, methamphetamine: 1 mg/kg, IP	(Canseco-Alba et al., 2019)
Nicotine, CB2R KO (Zimmer strain)	-	Conditioned place preference	∖ Nicotine-induced CPP (abolished). ∖ Nicotine self-administration.	Nicotine: 0.7 and 1 mg/kg, IP	(Navarrete et al., 2013)
Nicotine, CB2R KO (Deltagen strain)	-	Conditioned place preference	∖ Nicotine-induced CPP (abolished)	Nicotine: 0.5 mg/kg, SC	(Ignatowska-Jankowska et al., 2013)

Abbreviations: CB2xP, mice overexpressing CB2R; cKO, conditional knock-out ; CPP, Conditioned place preference ; CX3CR1, CX3C motif chemokine receptor 1 ; DAT, dopamine active transporter ; dose-dep, dose-dependent ; EtOH, ethanol ; IP, intra-peritoneal ; IV, intra-venous ; KO, knock-out ; PO, per os ; Ref, reference ; SC, sub-cutaneous ; VTA, Ventral tegmental area.

Supplementary Table 11. Analgesia. Behavioral outcome following CB2R activation or blockade is either enhanced (↗), decreased (↘) or unchanged (=). In some studies, the specificity of the ligand used has been challenged by the use of CBR2 KO mice (the “Deltagen strain”, with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), or the “Zimmer strain” with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
Pharmacological activation					
Healthy (Mouse)	GP1a (1-10 mg/kg, SC, local (dorsal flank))	Formalin pain assay (+/- morphine)	Analgesic effect (alone, non dose-dep). = morphine-induced analgesia	-	(Chen et al., 2019)
	GP1a (1-10 mg/kg, IP)	Carrageenan pain assay (+/- morphine)	No analgesic effect (alone). ↗ morphine-induced analgesia	-	(Chen et al., 2019)
	JWH-015 (0.1-100 mg/kg, IP)	Formalin flinch test (inflammatory pain)	Alone: analgesic effect (dose-dep). + ↗ morphine-induced analgesia	-	(Grenald et al., 2017)
	JWH-133 (20 mg/kg, IP)	Tail-flick test and hot plate test	= pain threshold	-	(Liu et al., 2017)
	HU-910 (30 mg/kg, IP)	Hot plate test	Analgesic effect	-	(Cortez et al., 2022)
	β-caryophyllene (5 mg/kg, PO), JWH-133 (10 mg/kg, SC)	Formalin pain assay	Analgesic effect	No effect at lower doses. Blocked with SR144528 (3 mg/kg, IP). No effect in KO mice (Zimmer)	(Klauke et al., 2014)
Healthy (Rat)	AM1241 (2.5 mg/kg, IP, twice daily for 6 days. Co-administered with morphine)	Hyperalgesia: method of Hargreaves. Allodynia: Von Frey filaments	↘ Morphine-mediated thermal hyperalgesia and tactile allodynia	Attenuated by AM630 (0.6 mg/kg, IP)	(Tumati et al., 2012)
	GW405833 (100 mg/kg, IP, 1 to 5h pre-test)	Tail flick and hot plate assay	Antinociceptive effect	No effect at 30 mg/kg	(Valenzano et al., 2005)
	JWH-015 (5 mg/kg, IP, 30, 60, 90 and 120 min before test)	Tail-flick test and hot plate test	Analgesic effect (alone). ↗ morphine-induced analgesia	-	(Altun et al., 2015)
Chronic inflammatory pain (Mouse)	JWH-015 (16-300 µg, subplantar administration)	Von Frey filaments, plantar test	↘ mechanical CFA-induced allodynia, ↘ thermal CFA-induced hyperalgesia (dose dep)	Blocked by AM630 (60 µg, subplantar)	(Negrete et al., 2011)
EAE (Mouse)	β-caryophyllene (50 mg/kg, PO, twice a day for 10 days)	Von Frey filaments	↘ mechanical hyperalgesia	-	(Alberti et al., 2017)
High Fat Diet (Mouse)	HU308 (4 mg/kg/day, PO, for 3 months)	Dynamic Plantar Aesthesiometer (Von Frey-like filaments), Hargreaves Test	↘ mechanical and thermal hypersensitivity	-	(Schmitz et al., 2016)
Incisional pain (Rat)	GW405833 (0.3-30 mg/kg, IP, 24h post injury)	Hind paw withdrawal thresholds (PWT)	↘ mechanical hyperalgesia	-	(Valenzano et al., 2005)
Inflammation (CFA, Rat)	GW405833 (0.01-30 mg/kg, IP, 24h post injury)	Hind paw withdrawal thresholds (PWT)	↘ mechanical hyperalgesia	No effect in KO mouse (Deltagen strain)	(Valenzano et al., 2005)
Neuropathic pain (PSN, Mouse)	β-caryophyllene (0,1-10 mg/kg daily, PO, starting 1 day post injury)	Von Frey filaments, Hargreaves test	↘ mechanical and thermal hyperalgesia	No effect in KO mice (Zimmer strain)	(Klauke et al., 2014)
	JWH-133 (0.3 mg/kg/inf, IV self-administration)	Plantar and von Frey tests	↘ mechanical hypersensitivity	No effect in KO mice (Zimmer strain)	(Cabañero et al., 2020)
Neuropathic pain (PSN, Rat)	GW405833 (0.3-30 mg/kg, IP, 24h post injury)	Hind paw withdrawal thresholds (PWT)	↘ mechanical hyperalgesia	-	(Valenzano et al., 2005)
Neuropathic pain (SNL, Rat)	AM1241 (0.1-3 mg/kg, IP, 15 min before testing)	Thermal and tactile Withdrawal Threshold	↘ tactile and thermal hypersensitivity (dose-dep)	Blocked by AM630 (0.3 mg/kg, IP)	(Ibrahim et al., 2003)
	AM1241 (1 µmol/h, Continuous intrathecal infusion for 7 days)	Von Frey filaments, radiant heat tests	Analgesic effect (↘ nerve ligation-induced mechanical allodynia and thermal hyperalgesia)	-	(Shiue et al., 2017)
	JWH-015 (1-10 mg/kg, IP, 1-week post-injury)	Elevated Plexiglas chambers from a thermal radiant heat source, calibrated von Frey filaments	Alone: analgesic effect (dose-dep). + ↗ morphine-induced analgesia	-	(Grenald et al., 2017)
Neuropathic pain (Retrovirus induced, Mouse)	JWH-015, JWH-133, GP1a or HU308 (5 mg/kg, IP, weekly starting at week 5 post injury.)	Mouse Metelectronic von Frey system	↘ allodynia (↘ mechanical hypersensitivity)	No effect 24h post agonist injection	(Sheng et al., 2019)
Post-operative pain (Rat)	JWH-015 (1-10 mg/kg, IP, 24h post-injury)	Elevated Plexiglas chambers from a thermal radiant heat source, calibrated von Frey filaments	Alone: analgesic effect (dose-dep). + ↗ morphine-induced analgesia	-	(Grenald et al., 2017)
CB2R BLOCKADE					
Pharmacological blockade					
Healthy (Rat)	JTE907 (5 mg/kg, IP)	Tail flick and hot plate test	= analgesia (alone). ↘ morphine-induced analgesia	-	(Altun et al., 2015)
Chronic Inflammatory Pain (Mouse)	AM630 (60 µg, Subplantar administration)	Von Frey filaments, plantar test	= mechanical CFA-induced allodynia and thermal hyperalgesia	-	(Negrete et al., 2011)
Genetic invalidation					
CB2R KO (Zimmer strain)	-	Plantar test, cold plate test, von Frey stimulation model	↗ basal nociceptive response	-	(Racz et al., 2008)
Cx3cr1-CB2R cKO	-	Tail flick test	= pain threshold	-	(Liu et al., 2020)
DAT-CB2R cKO	-	Hotplate and tail flick test	↗ pain threshold (tail flick but not hot plate test)	-	(Liu et al., 2017)
DAT-CB2R cKO	-	Tail flick test	↗ pain threshold	-	(Liu et al., 2020)

Neuropathic pain, CB2R KO (Zimmer strain)	Plantar test, cold plate test, von Frey stimulation model	↗ thermal hyperalgesia, mechanical and thermal allodynia	(Racz et al., 2008)
Neuropathic pain, Cell-specific deletion (CB2R KO BM chimeric mice)	Plantar test, cold plate test, von Frey stimulation model	↗ thermal hyperalgesia, mechanical and thermal allodynia	(Racz et al., 2008)

Abbreviations : BM, bone marrow ; CFA, complete Freund's adjuvant ; cKO, conditional knock-out ; CX3CR1, CX3C motif chemokine receptor 1 ; DAT, dopamine active transporter ; Dose-dep, dose-dependent ; EAE, experimental autoimmune encephalomyelitis ; IP, intra-peritoneal ; IV, intra-venous ; KO, knock-out ; PO, per os ; PSN, partial sciatic nerve ligation model ; ref, reference ; SNL, sciatic nerve ligation ; SC, sub-cutaneous.

Supplementary Table 12. Seizure activity. Behavioral outcome following CB2R activation or blockade is either enhanced (↗) or decreased (↘) or unchanged (=). In some studies, the specificity of the ligand used has been challenged by the use of CB2R KO mice (the "Deltagen strain", with a deletion of the sequence encoding the N-terminal part of the protein (The Jackson Laboratory, *Cnr2^{tm1Dgen}/J*, #005786), or the "Zimmer strain" with a deletion of the sequence encoding the C-terminal part of the protein (Buckley et al., 2000)).

MODEL	TREATMENT	TESTS	BEHAVIORAL OUTCOME	OTHER	REF
CB2R ACTIVATION					
<i>Pharmacological activation</i>					
MES (Mouse)	β-caryophyllene (30-300 mg/kg, IP, 30 min before MES)	MES: Corneal electrode, electric stimulus and hind limb extension measurement	↘ tonic-clonic seizure (66%)	-	(Tchekalarova et al., 2018)
PTZ (Mouse)	β-caryophyllene (100 mg/kg, IP, 60 min before PTZ)	IP injection of PTZ (60 mg/kg)	↗ latency to the first myoclonic jerk (MJ)	-	(Oliveira et al., 2016)
	β-caryophyllene (30-300 mg/kg, 4h before PTZ)	Subcutaneous (SC) PTZ seizure test	No effect	-	(Tchekalarova et al., 2018)
PTZ, PTZ+toxoplasmosis (Mouse)	HU308 (1-10 μg, icv, 10 min before PTZ)	Intravenous PTZ injection (10 mg/mL)	↘ seizure threshold	-	(Ghanbari et al., 2020)
PTZ (Rat)	AM1241 (0.01, 1 or 10 g/2 l, ICV microinfusion, 5 min before PTZ)	IP injection of PTZ (70 mg/kg)	↗ tonic-clonic seizure incidence and severity	Blocked by AM630 (1 mg/kg, IP)	(de Carvalho et al., 2016)
PTZ, DMCM (Rat)	HU-308 (2-10 mg/kg, IP, 20 min before PTZ)	SC injection of PTZ (100 mg/kg), or IP injection of DMCM (600 μg/kg)	No effect	-	(Huizenga et al., 2017)
Pilocarpine (Rat)	JWH-133 (1.5 mg/kg, IP, every 6h following SE)	IP administration of pilocarpine (375 mg/kg)	↗ latent period of first seizure attack, ↘ mortality	Blocked by AM630 (1.5 mg/kg, IP)	(Cao et al., 2021)
CB2R BLOCKADE					
<i>Pharmacological blockade</i>					
PTZ (Mouse)	SR144528 (30 min before PTZ)	SC injection of PTZ (100 mg/kg)	↘ latencies to the first MJ and generalized tonic-clonic seizure (GTCS)	No effect in KO mice (Deltagen strain)	(Shapiro et al., 2019)
PTZ, DMCM (Rat)	AM630 (2-10 mg/kg, IP, 20 min before PTZ)	SC injection of PTZ (100 mg/kg), or IP injection of DMCM (600 μg/kg)	No effect	-	(Huizenga et al., 2017)
PTZ, PTZ+toxoplasmosis (Mouse)	AM630 (1-5 μg, icv, 10 min before PTZ)	Intravenous PTZ injection (10 mg/mL)	↗ seizure threshold	-	(Ghanbari et al., 2020)
Genetic invalidation					
CB2R KO (Zimmer strain)		Alcohol (4 g/kg, IP.) induced HIS	↗ alcohol-induced HIC	-	(Ortega-Álvarez et al., 2015)
		Handling induced seizures	No seizure	-	(Rowley et al., 2017)
CB2R KO (^{+/+} and ^{-/-} Zimmer strain)		SC injection of PTZ (100 mg/kg)	↘ latencies to the first MJ and GTCS. ↘ % of mice reaching GTCS	-	(Shapiro et al., 2019)
CB2R KO (Deltagen strain)		6 Hz seizure induction paradigm	↗ average Racine score	-	(Shapiro et al., 2019)
CB1R/CB2R KO		Handling induced seizures	HIS in 27.6%. >1 spontaneous electrographic seizure in 80% of mice	-	(Rowley et al., 2017)

Abbreviations: DMCM, methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate ; GTCS, generalized tonic-clonic seizure ; HIS, handling-induced seizure ; ICV, intra-cerebroventricular ; IP, intra-peritoneal ; KO, knock-out ; MES, maximal electroshock seizure ; MP, myoclonic jerk ; PTZ, Pentylentetrazol ; Ref, reference ; SC, subcutaneous .