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Neuroprotection in Oxidative Stress-Related Neurodegenerative Diseases: Role of Endocannabinoid System Modulation

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Abstract

Significance: Redox imbalance may lead to overproduction of reactive oxygen and nitrogen species (ROS/RNS) and subsequent oxidative tissue damage, which is a critical event in the course of neurodegenerative diseases. It is still not fully elucidated, however, whether oxidative stress is the primary trigger or a consequence in the process of neurodegeneration.
Recent Advances: Increasing evidence suggests that oxidative stress is involved in the propagation of neuronal injury and consequent inflammatory response, which in concert promote development of pathological alterations characteristic of most common neurodegenerative diseases.
Critical Issues: Accumulating recent evidence also suggests that there is an important interplay between the lipid endocannabinoid system [ECS; comprising the main cannabinoid 1 and 2 receptors (CB1 and CB2), endocannabinoids, and their synthetic and metabolizing enzymes] and various key inflammatory and redox-dependent processes.
Future Directions: Targeting the ECS to modulate redox state-dependent cell death and to decrease consequent or preceding inflammatory response holds therapeutic potential in a multitude of oxidative stress-related acute or chronic neurodegenerative disorders from stroke and traumatic brain injury to Alzheimer's and Parkinson's diseases and multiple sclerosis, just to name a few, which will be discussed in this overview. *Antioxid. Redox Signal*. 29, 75–108.

Keywords: endocannabinoid, neuroprotection, oxidative/nitrative stress, neurodegeneration, free radicals, inflammation

Introduction

EVEN THOUGH THE THERAPEUTIC PROPERTIES of the plant *Cannabis sativa* (marijuana) have been known since ancient times, Δ^9-tetrahydrocannabinol (THC), the most abundant psychoactive constituent of hemp, was discovered only in the mid-60s (212). Since this important discovery, our knowledge on cannabinoids has greatly expanded by the identification of G protein-coupled cannabinoid 1 and 2 receptors (CB1 and CB2 receptor, respectively) (69, 204, 229) and by the elucidation of their intracellular signaling pathways (139, 321). Intriguingly, several small lipid mediators have been identified acting as endogenous cannabinoid receptor ligands, including arachidonoyl ethanolamide (or anandamide [AEA]) (70) and 2-arachidonoyl glycerol (2-AG) (211, 320). The synthesis and breakdown of these endogenous mediators have been extensively studied. During the past two decades, endocannabinoids *in vitro* have also been reported to act on other targets, including nuclear peroxisome proliferator-activated receptors (PPARs) (37), transient receptor potential vanilloid type 1 (TRPV1) (365) channel, and G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 119 (GPR119) [reviewed by Refs. (107, 270)].

Moreover, novel pathways of endocannabinoid metabolism have been discovered and different lipid mediators [*e.g.,* virodhamine (275), noladin ether (88),

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endocannabinoid-derived prostanoids, and peptide endocannabinoids] with endocannabinoid-like activity have been identified (172, 173, 220). In parallel with these important discoveries, it also became clear that modulation of the endocannabinoid system (ECS) holds great therapeutic potential in multiple neurodegenerative (and other) diseases [for review, see Refs. (187, 197, 249)]. Furthermore, various constituents of marijuana (*e.g.,* cannabidiol) (116) turned out to have important biological activities with translational potential for the treatment of human diseases (149, 187).

Dysregulation of endocannabinoid production and/or receptor expression have been reported under different pathophysiological conditions, including nociception (2, 290), emotional disorders (80, 114), energy imbalance (59, 81, 305), neurodegenerative diseases (5, 85, 87), cancer (337), diabetes and metabolic disorders (81, 247, 322), and cardiovascular disease (226, 280, 314) among others.

Accumulating evidence implicates enhanced oxidative/nitrative stress in the propagation of neuronal injury and consequent inflammatory response, which in concert promote development of pathological alterations and cell demise, characteristic of most common neurodegenerative diseases (the common mechanisms of redox-dependent processes involved in tissue injury are illustrated in Fig. 1).

Numerous studies also suggest an important interplay between the endocannabinoid lipid signaling system, plant-derived cannabinoids such as cannabidiol, and various redox-dependent processes (17, 138, 155, 227, 251, 336).

In this review, we focus on the role of the ECS and its therapeutic modulation in different oxidative stress-related neurodegenerative diseases.

Cannabinoid Signaling

CB1 receptor

The first endogenous cannabinoid receptor (CB1) has been originally identified in rat brain samples by Devane *et al.* (69). CB1 receptors are abundantly expressed in different areas of the brain, including cerebral cortex, hippocampus, caudate-putamen, substantia nigra pars reticulata, globus

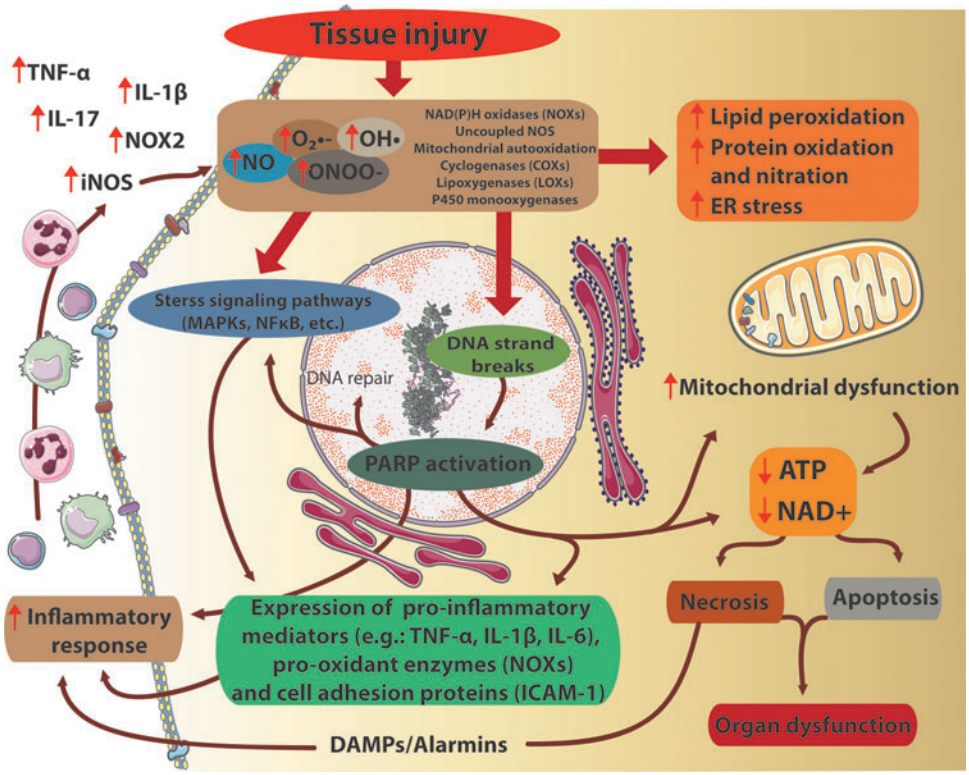

FIG. 1. Interplay of oxidative/nitrative stress, inflammation, and cell death pathways in tissue injury. Tissue injury ultimately results in excessive $O_2\bullet^-$, OH• production by NADPH oxidases (NOXs), uncoupled nitric oxide synthase (NOS) enzymes, mitochondrial autooxidation, lipoxigenases, or by the P450 monooxygenase system. Furthermore, in the presence of NO, the reactive free radical peroxynitrite ($ONOO^-$) can form as well. All these agents cause massive cell damage, lipid peroxidation, mitochondrial damage, endoplasmic reticulum (ER) stress, impaired calcium handling, and nitration of tyrosine residue of different proteins. Tyrosine nitration disturbs the structure of proteins, alterations in the catalytic activity of enzymes, and impairs cell signaling pathways. Moreover, $ONOO^-$ -induced DNA damage and the subsequent overactivation of the NAD^+-consuming poly(APD-ribose) polymerase-1 (PARP-1) enzyme compromise energy homeostasis. These detrimental effects of excessive formation of reactive oxygen/nitrogen species (ROS/RNS) ultimately lead to energy failure, neurotoxicity and neuronal death. On the other hand, ROS can enhance the formation of proinflammatory and pro-oxidant proteins by stimulation of MAPK or NFκB pathways, resulting in enhanced expression of proinflammatory mediators, facilitating the inflammatory response, leukocyte recruitment that contributes to an enhanced NO production by inducible NOS (iNOS), and further aggravation of ROS production. MAPK, mitogen-activated protein kinase; NAD^+, nicotinamide adenine dinucleotide; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; $O_2\bullet^-$, superoxide; OH•, hydroxyl radical. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

pallidus, entopeduncular nucleus, and cerebellum, as well as in the spinal cord (143).

The distribution of CB1 receptor in the central and peripheral nervous system reflects its pivotal functions: CB1 receptors are involved in modulation nociception, memory, anxiety, stress, depression, or addiction [reviewed by Ref. (222)]. At the cellular level, CB1 receptors are expressed by both central and peripheral neurons and also by non-neuronal cells such as astrocytes, microglial cells, cerebrovascular smooth muscle, and endothelial cells (25, 90, 101, 139, 281). CB1 receptors, located at central and peripheral nerve terminals, are able to modulate (inhibit) the release of excitatory and/or inhibitory neurotransmitters when activated (139, 161). On the other hand, CB1 receptors found on the postsynaptic neuron are able to control the activity of certain ligand-driven ion channels (*e.g., N*-methyl-D-aspartate [NMDA] receptors), thereby providing on-demand protection against acute excitotoxicity (202). Interestingly, CB1 receptors have been documented to present in the mitochondria of neurons and might be involved in modulation of neuronal energy homeostasis, revealing a new mechanism of action of CB1 receptor signaling in the brain (23, 125, 196). Moreover, activation of CB1 receptors in cat cerebrovascular smooth muscle cells has been shown to decrease the opening of L-type calcium channels (101), whereas in endothelial cells, it stimulates Ca^{2+} influx (108), suggesting that endocannabinoids might play an essential role in the regulation of cerebral arterial tone and reactivity in a CB1 receptor-dependent manner (25). Similarly, astrocytes expressing CB1 receptors might be involved in the regulation of local blood flow by producing nitric oxide (NO) and they also have the ability to regulate energy supply of neurons by increasing the rate of glucose oxidation and ketone body utilization [reviewed by Ref. (316)]. Low levels of functional CB1 receptors have been also described in the adipose tissue (59, 81), in liver (199), kidney (111, 155, 228), skeletal muscle and cardiovascular system (16, 177, 189, 226, 252), and certain immune cells, such as macrophages (77, 319).

CB1 receptors belong to the heterotrimeric G protein-coupled receptor superfamily, characterized by having seven transmembrane domains. Activation of CB1 receptors may lead to subsequent inhibition of adenylate cyclase, initiating depletion of intracellular cyclic adenosine monophosphate (cAMP) that results in reduction of protein kinase A (PKA) activity. On the other hand, it has been also reported that CB1 receptor may stimulate adenylate cyclase, thereby being able to increase intracellular cAMP levels (71).

CB1-driven modulation of PKA activity has impact on the activity of mitogen-activated protein kinase (MAPK) cascade that can influence cell fate, depending on the actual circumstances [reviewed by Ref. (36)]. Furthermore, CB1 receptors are also able to control ion channels in the neuronal cell membrane: upon G protein-coupled activation, cannabinoids may positively influence inwardly rectifying K^+ currents in a $\beta\gamma$-subunit-mediated manner, resulting in an elevated resting potential in neurons (113, 127). Moreover, neuronal calcium channels can be inhibited by cannabinoids in the same manner (113). Since the expression of CB1 in neurons is largely restricted to presynaptic terminals, the effects of cannabinoids on these ion channels suggest a pivotal role in modulating presynaptic functions and consequent neurotransmitter release (161).

CB2 receptor

The second main CB2 has been initially identified in immune and hematopoietic cells (94, 229). The abundant CB2 expression in immune cells suggests a unique immunomodulatory role of cannabinoids (195). Besides classic immune tissues (thymus, bone marrow, spleen), other peripheral tissues also show CB2 receptor expression [including the liver (158), pancreatic beta cells (156), bone (246), myocardium (18, 67, 219), and vasculature (280)]. Although the presence of CB2 receptors in microglial cells has been previously confirmed, their existence in neurons remains controversial (201, 253, 338, 342). Intriguingly, CB2 expression in microglia appears to be upregulated in certain oxidative stress-related neuropathologies, including Alzheimer's disease, multiple sclerosis (MS), or Parkinson's disease (9, 57, 254, 357); however, little is known about how free radicals are able to induce CB2 receptor expression.

The neuroprotective effect of CB2 agonists is associated with suppression of microglia activation, leading to inhibition of neurotoxic factor release and attenuation of neuronal cell damage (78, 167). Perivascular microglial cells show high CB2 expression, suggesting a potential role of CB2 in the regulation of cerebral blood flow and in preserving the integrity of the blood–brain barrier under neuroinflammatory conditions [reviewed by Ref. (25)].

Activation of CB2 ultimately results in cAMP decline, leading to reduced PKA activity with a consequent decrease in the inhibitory phosphorylation of MAPK cascade (36). By triggering the MAPK pathway, CB2-mediated cannabinoid signaling enables the influence of cell survival, proliferation, or stress response (139). In contrast to CB1 receptors, CB2 is not known to be able to modulate ion channel activity.

Increasing body of evidence suggests that endocannabinoids may serve as ligands for other receptors, including TRPV1 (365), PPARs (37) GPR55 (154), and GPR119 (248); however, the distinct role of these receptors in endocannabinoid signaling needs to be confirmed, particularly *in vivo* [reviewed by Refs. (22, 107)].

Emerging recent evidence also indicates that both CB1 and CB2 ligands may exhibit biased signaling [*e.g.,* certain ligands for the same receptor could affect distinct signaling pathways (181, 200, 311)]. Better understanding of these important differences may have very important implications for the development of future cannabinoid-based ligands for therapeutic use.

Endocannabinoid Metabolism

AEA, as the first described endocannabinoid, was identified in porcine brain in 1992 (70). The second key endocannabinoid, 2-AG, was discovered in canine intestines in the mid-90s (211, 320). AEA and 2-AG are the most abundant endocannabinoids that can be found in the central nervous system (CNS) as well as in all peripheral tissues.

Although endocannabinoids are thought to be produced on demand in response to certain stimuli, there is some evidence for their intracellular trafficking, storage, and even degradation in adiposomes (133, 160, 244) emphasizing a complex underlying mechanism of endocannabinoid signaling. 2-AG has been suggested to be the main endogenous agonist of CB2 receptors, whereas AEA has higher affinity to CB1 receptors (249). Moreover, it is known that 2-AG

appears in higher concentrations in tissues than AEA (321). Although the biosynthesis and metabolism of AEA and 2-AG have been well established, it is still unclear how these endocannabinoids are transported across the cell membrane. Increasing body of evidence suggests that AEA and 2-AG can be taken up by cells *via* facilitated diffusion in a protein transporter-mediated manner (132, 208, 242, 352).

Although pharmacological modulators have been designed to influence endocannabinoid uptake (Table 1), proteins that facilitate and control their transport have not been identified yet. Further studies are needed to clarify the underlying molecular mechanism of endocannabinoid transport across the cell membrane and to elucidate the role of other intracellular binding proteins involved in endocannabinoid trafficking [reviewed by Ref. (242)].

Table 1. Examples of Synthetic or Natural Compounds Modulating Endocannabinoid Metabolism and Signaling

Name of compounds	*Effect on eCB metabolism or CB receptors*	*Ref.*
Marijuana-derived compounds		
Δ^9-THC	Mixed cannabinoid receptor agonists	(253, 270)
Cannabidiol	Depending on assay/condition antagonist	(179, 209, 269–271)
Cannabigerol	of CB1/CB2 receptor agonists in CB1- and CB2-expressing cells or tissues	(46, 130, 270)
THCV	Depending on assay/condition CB2 agonist, CB1 inverse agonist	(269)
Endocannabinoids		
Anandamide	Agonists with higher selectivity for CB1	(253, 270)
2-AG	Agonists with higher selectivity for CB2	(253, 270)
Synthetic compounds		
HU-210	Mixed CB1/2 agonists	(269, 270)
WIN 55,212-2		(270)
CP 55940		(269, 270)
ACEA	Agonists with higher selectivity for CB1	(253, 268, 270)
Methanandamide	Agonists with higher selectivity for CB1, FAAH-resistant compound	(268, 270)
JWH-015	Agonists with higher selectivity for CB2	(253, 268, 270)
JWH-133		(253, 268, 270)
HU-910		(137)
HU-308		(253, 268, 270)
AM1241		(253, 270)
O-1966		(253, 345)
O-3853		(362)
LEI-101		(225)
SR141716A (Rimonabant)	CB1 inverse agonist/antagonist	(253, 270)
AM251		(268, 270)
Taranabant		(90, 270)
SR144528	CB2 inverse agonists/antagonists	(253, 268, 270)
AM630		(253, 268, 270)
JTE-907		(253, 268, 270)
PF-3845	FAAH inhibitors	(32, 323)
URB597		(128, 231)
URB937		(55)
BIA 10-2474		(326)
JNJ-42165279		(162)
JZL-184	MAGL inhibitors	(272, 359)
JZL-195 (dual FAAH, MAGL inhibitor)		(32, 162)
KML29		(144)
JZP 361		(262)
URB602		(56)
AM404	Inhibitors of the putative endocannabinoid membrane transporters	(221, 242)
The farinosone-C analog BSL-34		(39, 242)
OMDM-2		(52, 242)
UCM707		(52, 242)
VDM11		(66, 242)
KT-109	DAGL inhibitors	(140, 141)
LEI-105		(12)

2-AG, 2-arachidonoyl glycerol; ACEA, arachidonoyl-2-chloroethylamide; eCB, endocannabinoids; CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; DAGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; THC, Δ^9-tetrahydrocannabinol; THCV, Δ^9-tetrahydrocannabivarin.

AEA can be produced by neurons *in vitro* when stimulated with membrane-depolarizing agents (73). 2-AG can also be released by neurons in a Ca^{2+}-driven manner (317). Virtually all other cell types have been documented to be a source of endocannabinoids in the brain, including astrocytes and microglia, as well as cells of the cerebral vasculature (25, 341, 346). Recent studies also highlight that tissue injury promotes the release of endocannabinoids and eicosanoids (44, 243, 249). Furthermore, in the last few decades, a series of other endogenous small lipid mediators have been identified, evoking cannabinoid-like effects, including the polyunsaturated fatty acid derivatives dihomo-γ-linolenoyl ethanolamide and docosatetraenoyl ethanolamide (121); 2-AG ether (also known as noladin ether) (120); O-arachidonoyl ethanolamine (or virodhamine) (275); and N-arachidonoyl dopamine (NADA) (340). However, these endocannabinoid-like substances are synthesized in very low amounts and are found to be unstable molecules *in vivo*, with uncertain physiological role.

Additionally, it has been recently documented that the α-hemoglobin-derived peptide hemopressin (Hpα) is able to bind to the CB1 receptor *in vitro* and exerts CB1 receptor inverse agonistic effects (126). Hpα reduced food intake in rodents in a CB1 receptor-mediated manner (76). This finding suggests that not only polyunsaturated fatty acid derivatives but even certain proteins are able to induce cannabinoid-like effects (20, 109).

The complex metabolic root of AEA and 2-AG has been investigated in detail [for review, see Refs. (3, 198)]. The biosynthesis of AEA is mainly related to the hydrolysis of its membrane-bound precursor N-acylphosphatidylethanolamine (NAPE) by a phospholipase D (NAPE-PLD) (Fig. 2). This enzyme is able to synthetize a wide range of endogenous ethanolamines.

There are also other parallel pathways for the generation of AEA such as the phospholipase C (PLC)-mediated hydrolysis of NAPE yielding phosphoanandamide, which is then dephosphorylated by the tyrosine phosphatase protein tyrosine phosphatase, nonreceptor type 22 (PTPN22), and the inositol 5′ phosphatase SHIP1. Bacterial endotoxin-induced synthesis of anandamide in macrophages is mediated in this manner (190). Moreover, the sequential deacylation of NAPE by α/β-hydrolase 4 (Abhd4) results in the formation of glycerophospho-arachidonoyl ethanolamide. The subsequent cleavage of glycerophosphate residue can also contribute to the formation of anandamide (Fig. 2) (308).

The degradation of AEA is mediated by the membrane-linked fatty acid amide hydrolase (FAAH), yielding arachidonic acid and glycerol (Fig. 2). Additionally, increasing number of evidences emphasize that AEA may be metabolized by other enzymes, including cyclooxygenase-2 (COX-2), lipoxygenases, and members of the microsomal cytochrome P450 system [for review, see Refs. (4, 207, 310, 351, 353)].

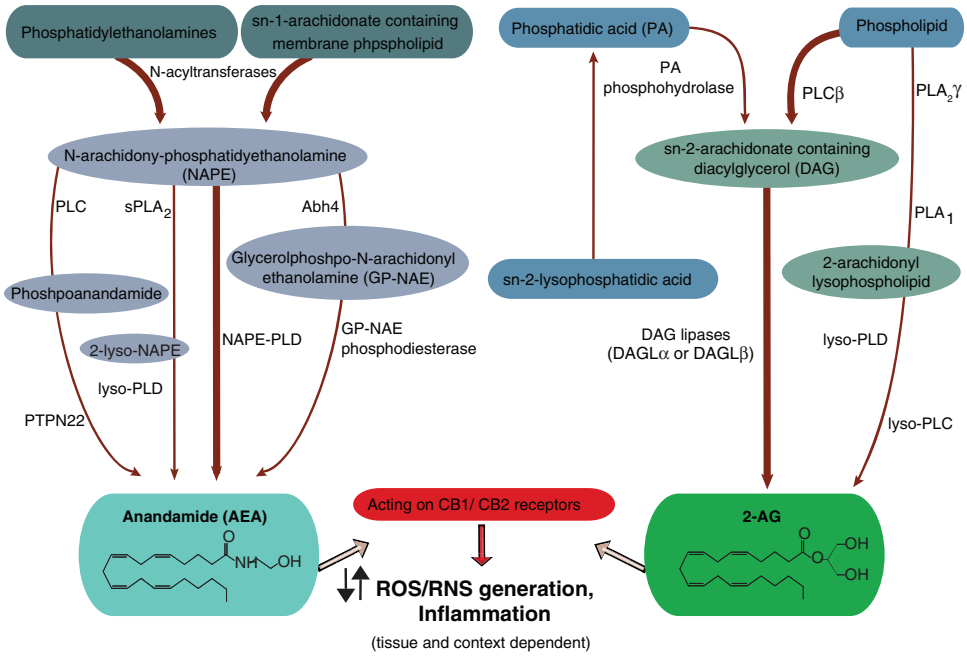

FIG. 2. Synthesis of the major endocannabinoids, AEA and 2-AG. The synthesis of AEA starts with the hydrolysis of the precursor N-acylphosphatidylethanolamine (NAPE) by a phospholipase D (NAPE-PLD). AEA can be formed from NAPE in a phospholipase C (PLC)-mediated manner as well, yielding phosphoanandamide, which is then dephosphorylated by the tyrosine phosphatase PTPN22. Moreover, the sequential deacylation of NAPE by α/β-hydrolase 4 (Abhd4) results in the formation of glycerophospho-arachidonoyl ethanolamide. The subsequent cleavage of glycerophosphate residue can also result in the formation of AEA. For the synthesis of 2-AG, the major precursor is the diacylglycerol (DAG), then DAG is converted to 2-AG by diacylglycerol lipase (DAGLα or DAGLβ) enzymes. On the other hand, 2-AG may be formed from other arachidonate-containing DAGs mediated by the calcium-independent phospholipase A2γ ($PLA_2\gamma$), thereby yielding a 2-arachidonoyl lysolipid that can be further converted to 2-AG by lysophospholipase D (lyso-PLD). Stimulating CB1/CB2 receptors, these endocannabinoids act oppositely in different tissues and might contribute to the formation of ROS/RNS. The most common biosynthetic pathways are indicated by *thick arrows*. 2-AG, 2-arachidonoyl glycerol; AEA, anandamide; CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; PTPN22, protein tyrosine phosphatase, nonreceptor type 22. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

Consistently, the resulting AEA derivatives are capable of promoting endocannabinoid-like effects (117, 168, 171, 306, 310, 313, 330).

For the biosynthesis of 2-AG, the major precursor is diacylglycerol (DAG), one of the main products of PLC (261); DAG is then further converted to 2-AG by diacylglycerol lipase (DAGL) enzyme (Fig. 2) (30). This enzyme has two different isoforms (DAGLα and DAGLβ) with a distinct tissue distribution pattern (72). 2-AG may also be formed independently from DAGLs: arachidonate containing DAGs can be liberated from the cell membrane by calcium-independent phospholipase A2γ (PLA$_2\gamma$), thereby yielding a 2-arachidonoyl lysolipid that can be further converted to 2-AG by lysophospholipase D (lyso-PLD) (152).

The serine hydrolase monoacylglycerol lipase (MAGL) is the key enzyme in the conversion of 2-AG to arachidonic acid and glycerol (74), although other enzymes are also thought to be involved in degradation of 2-AG such as the α/β hydrolase domains 6 and 12 (Abhd6 and Abhd12, respectively, see Fig. 3) (238). Similar to AEA, 2-AG may be a substrate for COX-2, for lipoxygenases and for microsomal cytochrome P450 enzymes, suggesting a significant interplay between endocannabinoid and eicosanoid signaling (142, 171–173, 220) (Fig. 3).

Implication of Endocannabinoid Signaling in Reactive Oxygen Species Formation

Intracellular source of free radicals

On the one hand, the detrimental effect of the excess of reactive oxygen and nitrogen species (ROS/RNS) is well recognized in various types of diseases/pathologies, including but not limited to atherosclerosis, certain neurodegenerative diseases (*e.g.,* Alzheimer's disease), diabetes and its complications, aging, various types of cancers, ischemia/reperfusion (I/R) injury, and inflammatory diseases [see review Refs. (50, 61, 148, 163, 230, 250, 283, 336)].

On the other hand, recent evidence highlights the distinct role of free radicals in different physiological processes such as cell growth (332), proliferation (40), and modulation of the activity of different enzymes and ion channels (15). Accordingly, the role of NO under physiological conditions has been widely studied. NO is physiologically produced by many cells of the brain, including neurons, endothelial cells, or glial cells (astrocytes, oligodendrocytes, and microglia) in a Ca^{2+}-calmodulin-dependent manner. Under normal conditions, neuronal and endothelial nitric oxide synthase (nNOS/NOS1 and eNOS/NOS3) and endothelial cells (eNOS or NOS3) produce a remarkable amount of NO in the nanomolar

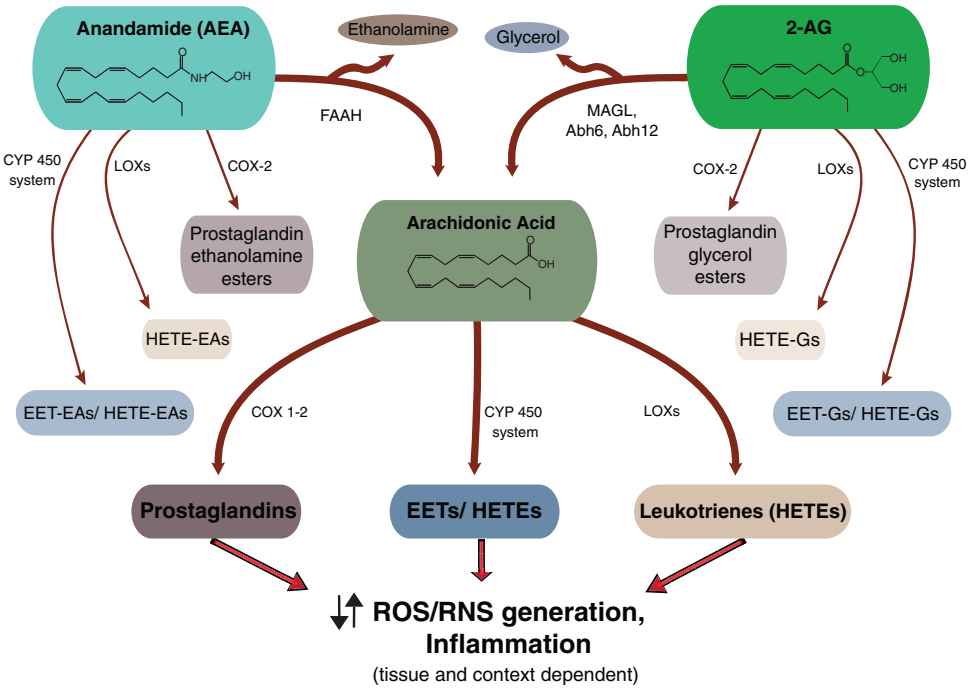

FIG. 3. Catabolism of AEA and 2-AG. The degradation of AEA is driven by the membrane-linked fatty acid amide hydrolase (FAAH) yielding arachidonic acid and glycerol. Then, arachidonic acid can be converted to prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids (HETEs) or epoxyeicosatrienoic acids (EETs) by COXs, LOXs, and by the microsomal cytochrome P450 system, respectively. On the other hand, AEA might be metabolized by cyclooxygenase-2 (COX-2), lipoxygenases (LOXs), or the members of the CYP 450 as well, yielding different AEA derivatives such as prostaglandin ethanolamine esters, hydroxyeicosatetraenoic ethanolamines (HETE-EAs), or epoxyeicosatrienoic ethanolamines (EET-EAs), respectively. Monoacylglycerol lipase (MAGL) is the key enzyme in the conversion of 2-AG to arachidonic acid and glycerol, although other enzymes are thought to be involved in the degradation of 2-AG such as the α/β hydrolase domains 6 and 12 (Abhd6 and Abhd12, respectively). Similarly to AEA, 2-AG may serve as a substrate for COX-2, for LOXs, and for microsomal cytochrome P450 enzymes (CYP 450) as well, yielding prostaglandin glycerol esters, hydroxyeicosatetraenoic glycerol (HETE-Gs), or epoxyeicosatrienoic glycerol (EET-Gs) derivatives, respectively. Thus, the degradation of endocannabinoids indirectly contributes to the formation of proinflammatory mediators. The most common catabolic pathways are highlighted by *thick arrows*. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

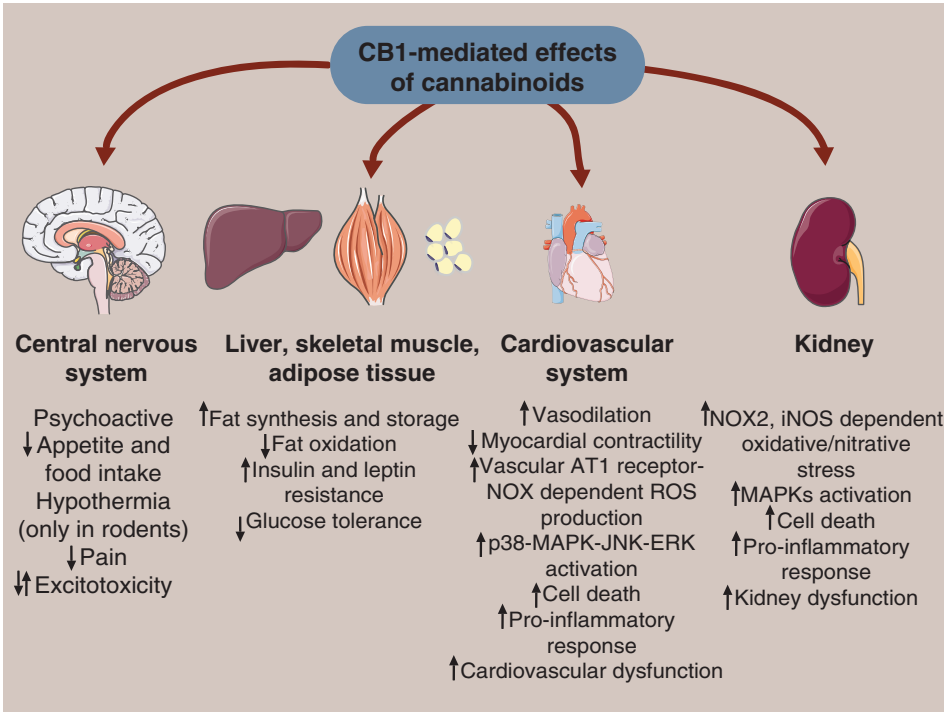

FIG. 4. CB1-mediated effects of cannabinoids in different tissues. Cannabinoids provoke multiple responses in tissues *via* stimulating CB1 receptor signaling. Triggering CB1 receptors in the central nervous system has psychoactive features and elicits appetite loss; hypothermia (observed only in rodents) decreases pain sensation and has multiple effects on excitotoxicity according to the cell-specific localization of CB1 receptor. Furthermore, in other organs involved in the regulation of lipid metabolism and energy homeostasis, cannabinoids trigger fat accumulation and decrease fatty acid oxidation, increase insulin and leptin resistance, and decrease glucose tolerance in a CB1 receptor-mediated manner. Moreover, the effect of CB1 receptor activation in the cardiovascular system has detrimental effects on myocardial contractility, decreases blood pressure by the initiation of vasodilation, impairs endothelial function leading to the formation and release of proinflammatory mediators, and facilitates vascular ROS/RNS production in an MAPK-JNK-ERK-mediated manner leading to cell death. Similarly, CB1 signaling in the kidney also leads to renal dysfunction by triggering NOX2 and iNOS expression that results in excessive oxidative/nitrative stress. Enhanced cell death can occur by MAPK activation leading to proinflammatory response. ERK, extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinase. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

range, which is essential for maintaining cerebral blood flow. NO is also involved in the regulation of neurotransmission, synaptic plasticity, and modulation of neuroendocrine functions since it can act as a second messenger activating soluble guanylyl cyclase, hence triggering the cyclic guanosine monophosphate-protein kinase G signaling axis (112, 218, 250).

Under various pathophysiological conditions associated with neuroinflammation, large amount of NO is produced in the brain due to the elevated expression of inducible nitric oxide synthase (iNOS/NOS2) in glial cells, infiltrating phagocytes, and vascular cells [reviewed by Ref. (250)]. This event plays a crucial role in the escalation of oxidative–nitrative stress and has deleterious effects on cell viability (Fig. 1).

Elevated NO level can contribute to the generation of peroxynitrite ($ONOO^-$), a powerful oxidant and nitrating species. NO by interacting with superoxide ($O_2\bullet^-$) generated by various sources (Fig. 1) leads to the rapid diffusion-limited formation of $ONOO^-$ (206, 218). The excessive formation of $ONOO^-$ promotes lipid peroxidation, mitochondrial damage, and depletion of glutathione, leading to impaired antioxidant capacity (Fig. 1). Tyrosine nitration by $ONOO^-$ disrupts the structure and function of various key proteins with the consequent formation of neoepitopes, alterations in the catalytic activity of enzymes, destruction of cytoskeleton, and impairment of cell signal pathways. $ONOO^-$-induced oxidative DNA damage and the subsequent overactivation of the nicotinamide adenine dinucleotide (NAD^+)-consuming nuclear enzyme poly(APD-ribose) polymerase-1 (PARP-1) compromise cellular energy homeostasis (Fig. 1). These detrimental effects of ROS/RNS-mediated cytotoxicity ultimately lead to energy failure, mitochondrial dysfunction, neurotoxicity, and neuronal death (145, 249, 297, 327).

In addition to impaired mitochondria, NADPH oxidase (NOX) enzymes can also be significant sources of ROS during tissue injury, similar to xanthine oxidoreductase, uncoupled eNOS, cytochrome P450 monooxygenases, and lipoxygenases (Fig. 3) [reviewed by Refs. (206, 292)]. A wide range of substances, including the inflammatory mediator arachidonic acid or oxidized low-density lipoprotein particles, can contribute to the association of NOX subunits leading to the consequent generation of $O_2\bullet^-$ (324). Moreover, superoxide may serve as a precursor for other free radicals, such as hydroxyl radical ($OH\bullet$) (Fig. 1). Furthermore, $OH\bullet$ can be formed from hydrogen peroxide (H_2O_2) in an Fe^{2+}-catalyzed nonenzymatic reaction (Fig. 1). Hydroxyl radical is a highly reactive compound compared with $O_2\bullet^-$, exhibiting a higher reaction rate with proteins, DNA, or

membrane lipids (mainly unsaturated fatty acids), thus it contributes to the generation of more free radicals and propagation of oxidative stress (206, 245, 250).

Interplay between ROS and endocannabinoid signaling

Oxidative stress is implicated in different neurodegenerative complications through the initiation of diverse signaling and transcriptional pathways [reviewed by Refs. (178, 335)]; however, little is known on how expression of enzymes is involved in endocannabinoid synthesis/degradation and cannabinoid receptors modulated/regulated by ROS. Based on a recent report, 2-AG biosynthesis may depend on the presence of NOX-derived oxyradicals (205). The authors have revealed that upon NOX activation, the elevated level of free radicals activated DAGLβ and resulted in an augmented level of 2-AG in macrophages. Nox2-overexpressing COS7 cells synthesized larger amounts of 2-AG when compared with controls (205). In the presence of either NOX or DAGLβ inhibitors in DAGL β-overexpressing COS7 cells, 2-AG levels were reduced (205), indicating a unique interplay between oxyradical production and endocannabinoid synthesis.

Increasing evidence also underscores the significance of endocannabinoid signaling in large number of pathological conditions characterized by enhanced ROS production [see review Refs. (249, 251)]. Activation of vascular CB1 receptors on endothelium and or smooth muscle cells by excessive levels of endocannabinoids during tissue injury may promote activation of p38 and JNK–MAPKs and increase ROS generation, thereby facilitating activation of cell death pathways (281) (Figs. 4 and 5). It has also been shown that AEA enhances prostaglandin E_2 (PGE_2) and 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) level, similar to free radical formation *via* enhancing COX-2 activity in lipopolysaccharide (LPS)-challenged astrocytes and microglial cells (237). Recent findings also highlight the ROS-generating effect of angiotensin II in endothelial and vascular smooth muscle cells (VSMCs) (240, 241, 325). A major consequence of angiotensin II receptor type 1 (AT1 receptor) stimulation by angiotensin II is the activation of NOX (240, 241). CB1 receptor activation has been shown to be more pronounced following AT1 receptor stimulation (329), suggesting a costimulatory effect of these two signaling pathways in ROS generation (Fig. 5).

Tiyerili *et al.* have shown that the CB1 receptor inverse agonist/antagonist rimonabant reduces angiotensin II-mediated NOX activity *in vivo* and *in vitro* (325).

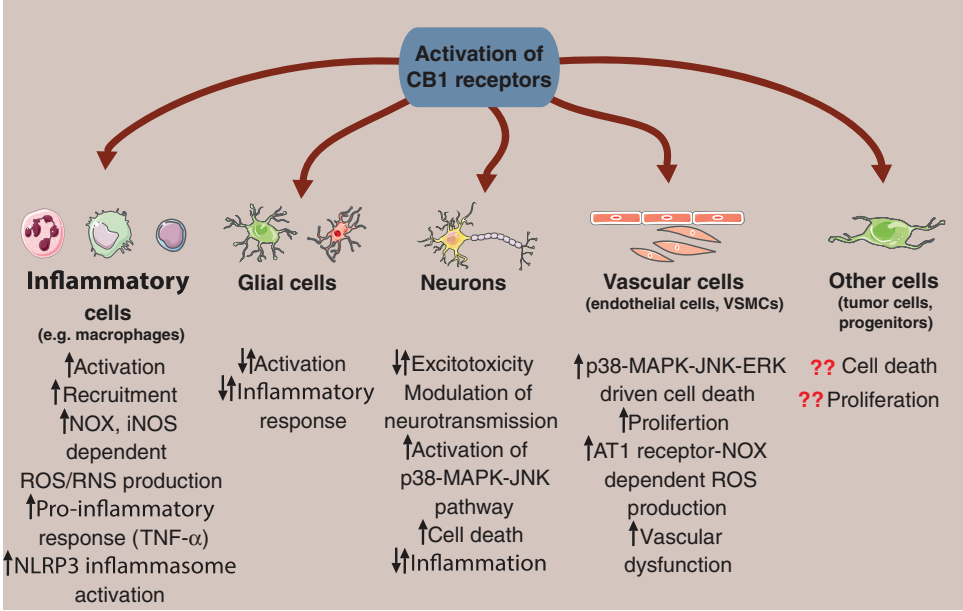

FIG. 5. Effects of the activation of CB1 receptor at cellular level. Activation of CB1 receptor signaling in presynaptic neurons can modulate neurotransmission by silencing the release of transmitters. Hence, CB1 receptors expressed in glutamatergic neurons can reduce glutamate-induced excitotoxicity, thereby attenuating cell death. In addition, CB1 receptor activation in GABAergic neurons might lead to a depressed inhibitory activity and concomitant overactivation of excitatory circuits. Moreover, CB1 stimulation might lead to p38-MAPK-JNK-dependent cell death and proinflammatory responses. In glial cells, cannabinoids can activate and facilitate inflammatory response, upregulate iNOS, and trigger ROS production. In contrast, attenuated activation and decreased ROS production of glial cells have been reported as well *via* the CB1-dependent stimulation of the cAMP-PKA axis. Furthermore, CB1 receptor signaling is able to promote the activation of inflammatory cells (*e.g.,* neutrophils and monocytes/macrophages), stimulate their recruitment, initiate ROS/RNS formation in an NOX and iNOS-dependent manner, provoke inflammasome activation, and proinflammatory response. In addition, CB1 receptor signaling promotes p38-MAPK-mediated cell death in the vasculature, enhances proliferation of vascular smooth muscle cells (VSMCs), and facilitates angiotensin II receptor type 1 (AT1)-mediated ROS formation *via* triggering NOX expression and activity in endothelial cells resulting in vascular dysfunction. However, the role of CB1 receptor activation in other cell types (*e.g.,* neuronal progenitors or tumor cells) is still unclear. *Question marks* indicate that the presence of CB1 receptor in certain cell types are still questionable. cAMP, cyclic adenosine monophosphate; NLRP3, NACHT, LRR, and PYD domain-containing protein 3 (also known as cryopyrin); PKA, protein kinase A. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

Furthermore, rimonabant decreased AT1 receptor expression in the aortic wall and cultured VSMCs (325).

Several studies also demonstrated that CB1 receptor activation promotes ROS generation and inflammatory response in macrophages, involving p38MAPK activation [reviewed in Ref. (315)].

In contrast, the neuroprotective role of CB1 receptor has been documented in a mouse model of Parkinson's disease (54). This neuroprotection by nonselective CB1 agonists (WIN55,212-2 and HU210) was accompanied by increased survival of nigrostriatal dopaminergic neurons in the striatum, suppression of NOX and ROS production, and reduced expression of proinflammatory cytokines from activated microglia. Similarly, it has been also reported that AEA protected hippocampal neurons from oxidative injury by decreasing intracellular ROS and lowering the expression of NOX2 in a CB1 receptor-mediated manner. All these effects were abolished by simultaneous administration of CB1 antagonist AM251 or by CB1-siRNA (153). Because of this great diversity of results, further studies are required to uncover the contribution of CB1 receptor signaling to ROS formation, which is apparently context and cell-type dependent and may be a secondary/indirect consequence of various processes (Figs. 4 and 5).

Activation of CB2 attenuates vascular inflammation by decreasing endothelial expression of adhesion molecules (*e.g.,* intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1]) and transendothelial migration of leukocytes. It also decreases pathological microglial activation, thereby indirectly attenuating oxidative/nitrative stress and subsequent cell death (253, 280, 314).

An enhanced CB2 expression was demonstrated in cerebral vessels of human brains from subjects with HIV-1 encephalitis (108, 282). In a rodent model of LPS-induced encephalitis, leukocyte-endothelial adhesion was also evaluated on the surface of cortical vessels, which was significantly inhibited by CB2 receptor agonists. CB2 activation reduced the expression of adhesion molecules required for leukocyte recruitment and upregulated tight junction protein expression, thereby improving blood–brain barrier function (267, 282, 289).

CB2 receptor stimulation in CNS was also shown to reduce iNOS expression and NO production in activated microglial cells *via* inhibition of extracellular signal-regulated kinase (ERK)-1/2 phosphorylation in CNS inflammation (214) (Figs. 6 and 7). The nonselective cannabinoid receptor agonist WIN 55,212-2 inhibited HIV-1 envelope glycoprotein gp120-induced interleukin (IL)-1β production and synapse loss that was reversed by CB2 receptor antagonist (164). These results suggest that CB2 agonists may have therapeutic potential in HIV-1-associated neurocognitive disorder commonly presented in patients with AIDS.

All the abovementioned findings emphasize the potent anti-inflammatory effect of CB2 signaling in immune cells, which is associated with attenuated ROS production and reduced neuronal cell death (Figs. 6 and 7).

Notably, the nonpsychoactive marijuana-derived cannabinoid, cannabidiol (CBD), has been shown to exert potent neuroprotective effects against neuroinflammation. CBD was

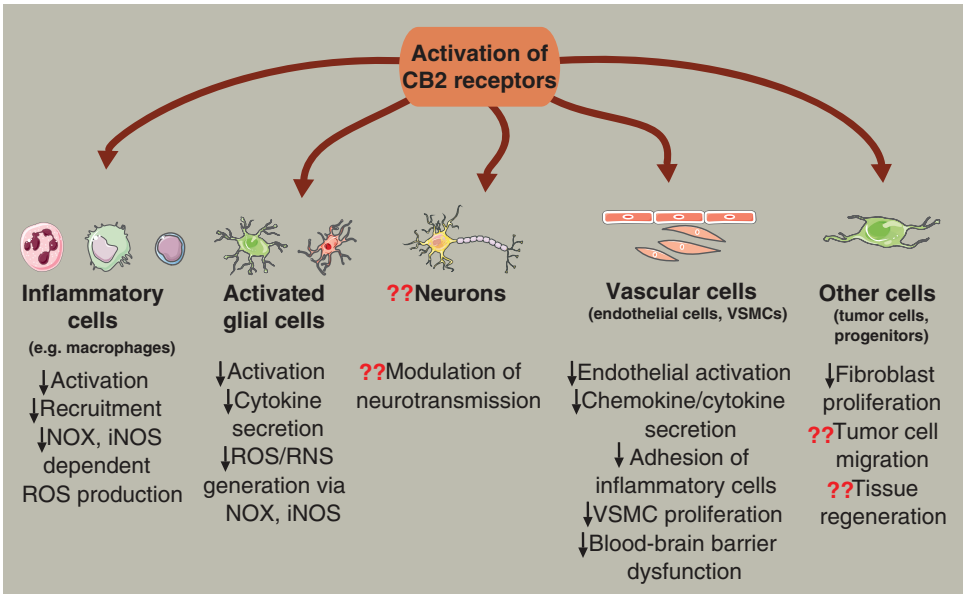

FIG. 6. Effects of the activation of CB2 receptor at cellular level. Expression of CB2 receptor and its role in the modulation of neurotransmission are still a matter of debate; however, it is well known that CB2 receptor messenger ribonucleic acid (mRNA) levels rise during the activation of microglial and/or astroglial cells. Moreover, stimulation of CB2 receptor signaling is able to attenuate glial activation in neuroinflammation. Furthermore, CB2 activation can reduce the release of cytokines/chemokines (TNF-α, IL-1β) originated from glial cells and diminish the formation of ROS/RNS produced by NOX and iNOS. In addition, CB2 receptor stimulation attenuates leukocyte recruitment and mitigates inflammation and ROS/RNS production in inflammatory cells as well. Moreover, in the vasculature, CB2 receptor activation can attenuate endothelial activation, cytokine/chemokine release, inflammatory cell adhesion and transmigration, VSMC proliferation, and blood–brain barrier dysfunction. In other cell types, it has been reported that fibroblast proliferation can be decreased in a CB2 receptor-mediated manner; however, its role in tissue regeneration or in tumor cell formation and migration is still questionable. *Question marks* show that the involvement of CB2 receptor in certain processes is still a matter of debate. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

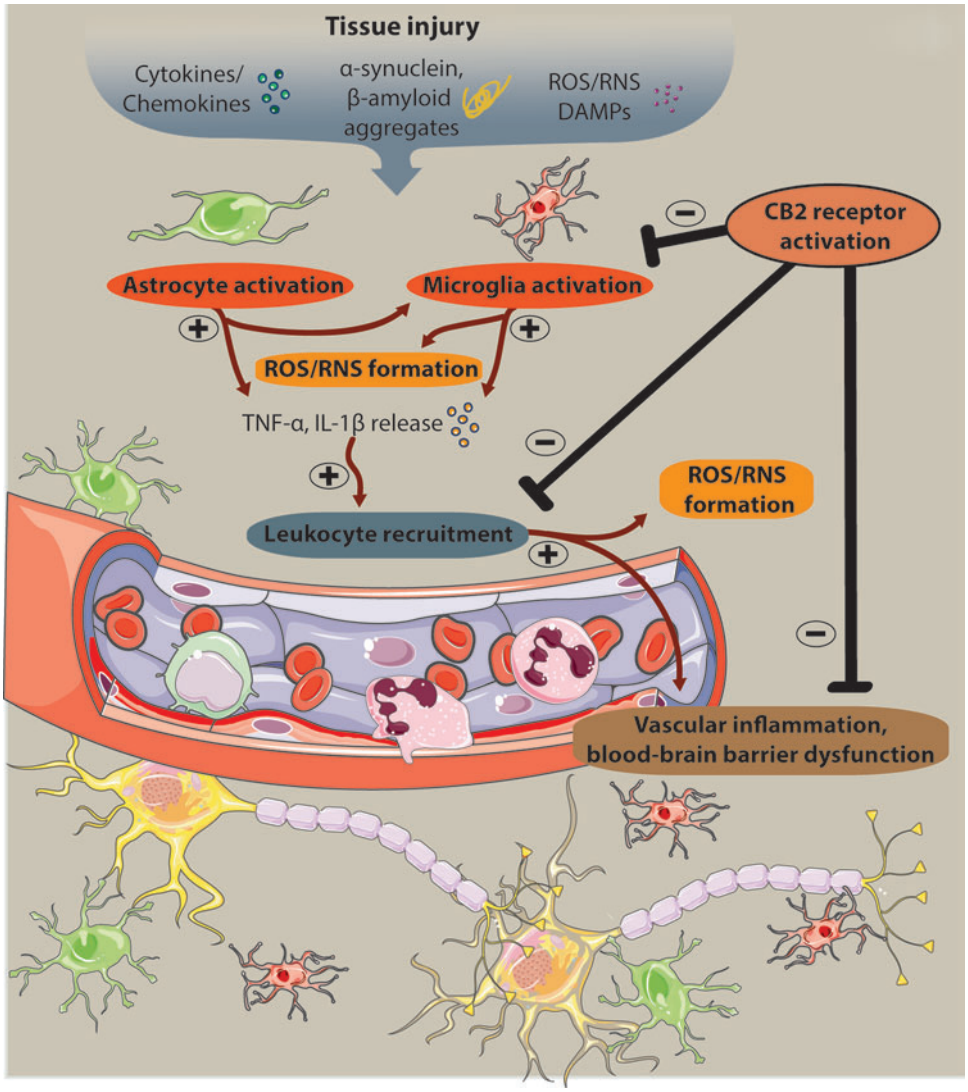

FIG. 7. The role of cannabinoid signaling in oxidative stress-related neurodegenerative diseases. The involvement of innate immune system in the development and progression of different neuroinflammatory diseases is well described. Activation of microglial and/or astroglial cells is a key event during neuroinflammation and is triggered by numerous factors such as proinflammatory cytokines/chemokines, α-synuclein, β-amyloid aggregates, elevated levels of ROS/RNS, or by damage-associated molecular patterns (DAMPs) derived from necrotic cells. Following glial activation, soluble factors (TNF-α, IL-1β) trigger leukocyte recruitment and contribute to the aggravation of inflammation, production of ROS/RNS, and neuronal death. Hence, drugs targeting CB2 receptors have multiple actions on ROS-mediated neuroinflammation since it can decrease ROS/RNS production in activated glial cells, attenuate vascular inflammation, improve blood–brain barrier function, and prevent leukocyte recruitment, thereby attenuating neuronal cell death. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

shown to prevent H_2O_2-induced oxidative damage in neuronal cultures and was more protective against glutamate-induced neurotoxicity than either ascorbate or alpha-tocopherol, emphasizing its potent antioxidant and anti-inflammatory effects (116).

Similarly, Mecha *et al.* have reported that CBD protected oligodendrocyte progenitor cells challenged by LPS/interferon (IFN)-γ (210). CBD effectively decreased ROS production, caspase-3 activation, and attenuated endoplasmic reticulum stress-induced apoptosis *via* mechanisms that do not depend on CB1, CB2, TRPV1, or PPARγ signaling (210), suggesting a unique cannabinoid receptor-independent neuroprotective mechanism most likely related to the direct antioxidant and anti-inflammatory effects of this compound.

Role of Endocannabinoids in the Pathophysiology of Oxidative Stress-Related Neurodegenerative Disorders

Stroke

Acute ischemic stroke is one of the leading causes of death worldwide and a prominent cause of hospitalization with acquired disability. Ischemic stroke results from the reduction of cerebral blood flow due to a transient or permanent thrombotic occlusion of a major cerebral artery. A complex cascade of molecular events is activated during cerebral ischemia that eventually leads to neuronal cell death (Fig. 1).

The immediate consequence of ischemia is a significant depletion of tissue adenosine triphosphate (ATP) levels that

is associated with dissipation of ionic gradients across the neuronal cell membrane normally maintained by Na^+/K^+-ATPases. The dysregulation of normal ionic homeostasis ultimately leads to rapid depolarization of neurons and glia, followed by activation of voltage-dependent Ca^{2+} channels and Ca^{2+} overload (188). These events induce the release and accumulation of excitatory neurotransmitters (mainly glutamate) in the synaptic cleft, triggering the activation of two distinct ionotropic receptors, the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. NMDA receptors exacerbate Ca^{2+} overload allowing inward Ca^{2+} transport, whereas AMPA receptor activation facilitates intracellular Na^+ accumulation and a consequent brain edema (188). The pathological alterations elicited by the actions of glutamate on these receptors are also known as excitotoxicity.

The massive increase in intracellular Ca^{2+} contributes to the activation of various enzymes, including phospholipases, cyclooxygenases, NOS, and proteolytic enzymes. Moreover, it also stimulates the release of free radicals, which triggers lipid peroxidation, DNA injury, and mitochondrial dysfunction that can eventually jeopardize cellular function and survival (188, 288).

Intracellular calcium overload and oxidative stress promote the activation of different transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), hypoxia-inducible factor 1 (HIF-1), and signal transducer and activator of transcription 3 (STAT3). Thus, they trigger the production of inflammatory cytokines (tumor necrosis factor alpha [TNF-α], IL-1β), increased expression of iNOS and COX-2, adhesion molecules (ICAM-1, selectins), and the recruitment of activated leukocytes culminating in local tissue inflammation (75).

It has been widely accepted that endocannabinoids can be produced in response to certain stimuli, for example, overactivation of the glutamatergic NMDA and AMPA receptors (119, 159, 161). Recent findings have revealed that cerebral ischemia is associated with the increase of tissue N-acetylethanolamine and endocannabinoid levels; however, the course of presented endocannabinoid mediators highly depends on the model and the type of brain insult (Tables 2 and 3) (82, 98, 118, 232, 236, 257).

Although initial studies described an endocannabinoid-driven neuroprotection against cerebral ischemia, the exact role of endocannabinoids in focal ischemic insult is still controversial. Shen and his coworkers have reported cannabinoid receptor-mediated silencing of excitatory neuronal activity in cultured rat hippocampal neurons (302). The nonselective cannabinoid receptor agonist WIN 55,212-2 reduced neuronal cell death in a CB1-dependent manner *via* attenuated presynaptic glutamate release, thereby decreasing excitotoxicity and cell death (115, 161, 165, 302). WIN 55,212-2 was also able to reduce infarct volumes *in vivo* when administered before the induction of both global and focal cerebral ischemia (233).

Interestingly, activation of the recently discovered mitochondrial CB1 receptor by using arachidonoyl-2-chloroethylamide (ACEA) has been shown to exert neuroprotection against ischemia/reperfusion injury *via* decreasing oxidative stress, lactate dehydrogenase release, and caspase-3 activation *in vitro*, as well as by ameliorating neurological scores *in vivo.* ACEA-induced neuroprotection was completely abolished by the selective cell-permeant CB1 receptor antagonist AM251, but only partially diminished by the selective cell-impermeant CB1 receptor antagonist hemopressin (196), suggesting that mitochondrial CB1 expression plays a unique role in cannabinoid-driven neuroprotection and might directly regulate mitochondrial ROS formation under this pathological condition.

Furthermore, it has been also documented that CB1 activation by using another agonist (HU-210) conferred neuroprotection in a permanent focal middle cerebral ischemia model (185). Infarct volumes and motor disability were significantly reduced in animals treated with HU-210. The neuroprotective effect of HU-210 was partially reversed by coadministration of rimonabant. However, it was completely abolished by maintaining the core temperature of treated animals to the levels observed in controls, suggesting that it was mediated by CB1-dependent hypothermia. Even though cannabinoids are able to lower blood pressure, reduction of cerebral blood flow was not observed in the border zone by the CB1 receptor agonist HU-210 following permanent middle cerebral artery occlusion (185).

Consistently, it has been also documented that $CB1^{-/-}$ mice had increased mortality, increased infarct volume, and severe neurological defects following permanent focal cerebral ischemia. The excitation-induced neurotoxicity was also more severe in CB1-deficient mice compared with their wild-type littermates (259).

In contrast, evidence supporting the detrimental effect of CB1 signaling following transient middle cerebral artery occlusion has been shown by Muthian *et al.* (232). The authors have revealed that the detrimental effect of CB1 receptor activation was mediated by the acutely elevated brain AEA levels following the insult. They also showed that administration of CB1 receptor inverse agonist/antagonist rimonabant before middle cerebral ischemia exhibited a significant reduction in infarct volume and a remarkable improvement in neurological function compared with the vehicle-treated group. In line with this finding, others have also shown the neuroprotective effect of CB1 receptor blockade in focal cerebral ischemia models emphasizing different pathways in the protection of rimonabant against cerebral ischemia (265, 361). The plausible explanation for the opposing effects of CB1 inhibition *versus* studying CB1 knockouts is still unclear (could be, in part, explained by poor temperature control and central hypothermic effects of CB1 agonists in rodents); however, further studies are required for the clarification of actual status of CB1-related endocannabinoid signaling in cerebral ischemia.

Concerning the effect of CB2-mediated signaling, it has been documented in an elegant study performed by Zhang and his coworkers that activation of CB2 receptors by using CB2 agonist, O-1966, reduced inflammatory responses (leukocyte adhesion and invasion) and improved neurologic function following insult in cerebral ischemia/reperfusion injury (Figs. 6 and 7). Moreover, CB2 receptor knockout mice showed larger cerebral infarct volumes and worse neurological function compared with wild-type mice (360).

In another study, the coadministration of rimonabant and O-1966 exerted greater protection against cerebral ischemia/reperfusion injury compared with CB2 receptor activation alone, although the neurological scores were rather similar in these groups (361). Consequently, CB2 receptor activation

Table 2. *In Vitro* Evidence of the Interplay of Endocannabinoids and Oxidative/Nitrative Stress

Model	*Changes in eCB level*	*Changes in cannabinoid receptor expression*	*Changes in oxidative stress markers following eCB targeted treatment*	*Ref.*
Cultured mouse cortical neurons	Not measured	Not measured	CB1/CB2 activation by WIN 55,212-2 or by AEA reduced neuronal cell death and attenuated oxidative stress induced by Fe^{2+}. Protection was abolished by the administration of rimonabant.	(165)
PC12 pheochromocytoma cell line	Not measured	Not measured	6-OHDA-induced cell death was attenuated by AEA.	(217)
Rat glioma C6.9 cell line and primary rat cortical astrocytes	Not measured	Not measured	CBD treatment induced apoptosis in glioma cells *via* stimulation of ceramide synthesis; however, It did not affect viability of primary astrocytes. Long-term CBD incubation prevented H_2O_2-induced cell loss and abrogated sensitization to oxidative stress in serum-deprived astrocytes.	(45)
C6 glioma cell line	Not measured	Not measured	THC dose-dependently increased cell damage and death in the presence of agents generating ROS in a CB1-mediated manner.	(110)
Murine microglial BV-2 cell line or primary rat microglia culture	Not measured	High expression of CB2 in both BV-2 cells and primary microglia cells	Both CB1 and CB2 agonists attenuated LPS-induced iNOS expression, NO production and ROS generation.	(287)
Microglial BV-2 cell line	Not measured	Not measured	CBD and THC repressed the expression of several proinflammatory genes (CCL2, CCL7, CXCL14, CCL6, and CCL9). Interestingly, the authors found and increased ROS formation in BV-2 cells induced by CBD *via* the upregulation of genes involved in redox homeostasis.	(157)
Microglial BV-2 cell line	Not measured	Not measured	CBD and THC decreased the production and release of IL-1β, IL-6, and IFN-β following LPS challenge. CBD, but not THC, reduced the activity of the NF-κB pathway and activated STAT3 signaling.	(175)
Primary mouse microglia culture	Not measured	Not measured	NADA prevented ROS formation and PGE_2 generation, whereas AEA exerted the opposite effects in LPS-primed primary microglial cells.	(237)
Human primary mDC and pDC	High expression of FAAH in pDC cells derived from MS patients.	High expression of CB2 in mDCs and pDCs originated from MS subjects.	mDCs produced high level of IL-6 and IL-12, whereas pDCs accounted for lower levels of IFN-γ in MS subjects compared with healthy controls. AEA inhibited cytokine production of dendritic cells as well as their ability to generate Th1 and Th17 lineages.	(53)

6-OHDA, 6-hydroxydopamine; AEA, anandamide; CBD, cannabidiol; CCL, C-C motif chemokine; H_2O_2, hydrogen peroxide; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; mDC, myeloid dendritic cell; MS, multiple sclerosis; NADA, N-arachidonoyl dopamine; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; pDC, plasmacytoid dendritic cell; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; Th1, T helper 1; Th17, T helper 17.

Table 3. Implication of Targeting the Endocannabinoid System in Oxidative Stress-Related Neurodegenerative Diseases

Model	*Changes in eCB level*	*Changes in cannabinoid receptor expression*	*Drug used*	*Observation*	*Changes in oxidative stress markers following eCB targeted treatment*	*Ref.*
Mouse model of permanent focal cerebral ischemia	Not measured	Not measured	Not used	Increased infarct volume was found in $CB1^{-/-}$ mice compared with wild-type mice.	Not measured	(259)
Rat model of cerebral ischemia	Not measured	Not measured	CB1 activation by HU-210	HU-210 decreased motor disability and infarct volume that were abolished by the administration of rimonabant.	Not measured	(185)
	Significantly elevated brain AEA level. 2-AG was slightly increased	Not measured	CB1/CB2 activation by WIN 55,212-2 CB1 blockade by either rimonabant or LY320105	Rimonabant or LY320105 reduced cerebral infarct volume and neuronal cell death, whereas the administration of WIN 55,212-2 was ineffective.	Not measured	(232)
	Not measured	CB1 receptor expression was unchanged in cultured cortical neurons following hypoxia	CB1/CB2 activation by WIN 55,212-2	WIN 55,212-2 treatment reduced cerebral infarct volume and neuronal cell death. Improved neurological function was also noted.	Not measured	(233)
Mouse model of cerebral (I/R) injury	Not measured	Not measured	CB2 activation by O-1966	The treatment improved neurologic function and reduced brain edema induced by transient mid cerebral artery occlusion.	O-1966 reduced inflammatory responses and leukocyte recruitment.	(356)
Rat and porcine model of brain hypoxia	Not measured	Not measured	CBD	CBD treatment improved neuronal cell survival in newborn rats exposed to short-term hypoxia	Reduced expression of inflammatory mediators (TNF-α), improved antioxidant capacity.	(263, 264)
Mouse model of TBI	Elevated brain 2-AG following CHI	Not measured	Exogenous 2-AG or rimonabant	2-AG exerted neuroprotection by inhibiting the early inflammatory response, improved blood–brain barrier function. Moreover, administration of 2-AG improved neurological performance and decreased edema that was completely abolished in $CB1^{-/-}$ mice.	2-AG inhibited TNF-α, IL-1β, and IL-6 expression and improved brain antioxidant capacity after CHI.	(255, 256)
	Not measured	Not measured	CB2 receptor stimulation with 0–1966 and JWH-133	CB2 stimulation reduced blood–brain barrier permeability and suppressed microglial activation and monocyte recruitment.	CB2 receptor agonist decreased TNF-α protein level, attenuated vascular ICAM-1 expression, and decreased iNOS expression.	(6, 79)
	Not measured	Not measured	MAGL inhibitor JZL-184	Inhibition of 2-AG metabolism promoted neurologic recovery: spatial learning and memory were improved following TBI	JZL-184 treatment reduced the production of proinflammatory cytokines, astroglial activation.	(359)
	Drug treatment increased brain AEA level	Not measured	The selective FAAH inhibitor PF3845	PF3845 attenuated TBI-induced anxiety, reduced deficits in hippocampus-dependent memory performance and in fine motor coordination *via* activation of CB1 and CB2 receptors	PF3845 upregulated the expression of the antiapoptotic Bcl-2 and Hsp70/72 proteins, decreased caspase-3 activity, and suppressed COX-2 and iNOS expression	(323)

(*continued*)

TABLE 3. (CONTINUED)

Model	*Changes in eCB level*	*Changes in cannabinoid receptor expression*	*Drug used*	*Observation*	*Changes in oxidative stress markers following eCB targeted treatment*	*Ref.*
Mouse model of experimental MS	Not measured	Not measured	Dexanabinol	Dexanabinol significantly reduced maximal EAE score when given once at the onset of disease.	Dexanabinol reduced inflammatory response in the brain and spinal cord in ALS mice.	(1)
	Not measured	Not measured	$CB1^{-/-}$ mice	Neurofilament and myelin basic protein levels decreased over the course of experimental ALS. In addition, concomitant neuronal/axonal loss and demyelination were observed.	$CB1^{-/-}$ mice displayed increased Caspase-3 activation	(150)
	Not measured	Not measured	CBD	Administration of CBD at the onset of EEA reduced axonal loss, infiltration of T cells, and microglial activation.	CBD treatment was accompanied instead reduced microglial activation and T cell recruitment in the spinal cord.	(174)
Mouse model of experimental ALS	Increased spinal 2-AG and AEA level	Not measured	Not used	Progressive neuronal damage increased endocannabinoid production in ALS mice.	Not measured	(347)
AβPP/PS1 mice and wild-type littermate	Not measured	Not measured	CB2 receptor activation by JWH-133.	JWH-133 induced cognitive improvement in AβPP/PS1 mice.	JWH-133 reduced microglial IL-1β, IL-6, IL-10, and TNF-α production increased 4-HNE content and enhanced the expression of SOD1 and SOD2 around senile plaques.	(10)
Mouse model of Alzheimer's disease induced by β-amyloid fragment injection	Increased hippocampal 2-AG, but not AEA, level	Enhanced CB2, but not CB1, expression in the treated hemisphere	The endocannabinoid reuptake inhibitor VDM11	β-Amyloid fragment injection significantly increased hippocampal cell loss. VDM11 improved memory retention.	VDM11 treatment decreased iNOS, COX-2, and Caspase-3 expression following β-amyloid fragment injection.	(333)
Postmortem human brain tissues from patients with Alzheimer's disease	Enhanced FAAH expression in glial cells associated with senile plaque	Enhanced CB2 expression in glial cells associated with senile plaque	Not used	FAAH and CB2 receptors have an overexpressed feature in glial cells linked to the inflammatory process that accompanied with Alzheimer's disease.	Not measured	(24)
Rodent model of experimental Parkinson's disease induced by 6-OHDA	Not measured	CB1 receptor expression was unchanged in lesioned brain regions. CB2 expression was not measured	THC/CBD treatment	Chronic administration of either THC or CBD significantly decreased neurodegeneration produced by a unilateral injection of 6-OHDA into the medial forebrain bundle.	Not measured	(184)
	Not measured	Not measured	ACEA; WIN 55,212-2; HU-308; AM-404; or CBD treatment	Daily administration of the CB1 agonist ACEA or WIN 55,212-2 did not reverse neuronal damage, whereas HU-308 produced a slight recovery. AM-404 produced a marked recovery of 6-OHDA-induced depletion.	SOD expression was increased by CBD in the affected region compared with vehicle control.	(97)

(*continued*)

TABLE 3. (CONTINUED)

Model	*Changes in eCB level*	*Changes in cannabinoid receptor expression*	*Drug used*	*Observation*	*Changes in oxidative stress markers following eCB targeted treatment*	*Ref.*
Mouse model of experimental Parkinson's disease induced by MPTP	Not measured	Not measured	The nonselective cannabinoid receptor agonist WIN 55,212-2	WIN 55,212-2 exerted neuroprotection against MPTP-induced loss of nigrostriatal dopaminergic neurons This protection was independent from CB1 receptor activation.	Not measured	(276)
	Not measured	Not measured	WIN 55,212-2 and HU-210 treatment	WIN 55,212-2 and HU-210 attenuated nigrostriatal neuronal cell loss.	Decreased NOX activation, reduced IL-1β and TNF-α expression levels were observed mediated *via* CB1 receptor.	(54)
Mouse model of experimental Huntington's disease induced by malonate injection	Not measured	Increased expression of CB2 following injection of malonate	ACEA; HU-308 or CBD treatment	HU-308 and CBD treatment attenuated malonate-induced cell loss likely through a mechanism involving glial cells. ACEA treatment failed to improve cell death.	Activation of CB2 receptors significantly reduced the levels of TNF-α.	(295)

4-HNE, 4-hydroxynonenal; ACEA, arachidonoyl-2-chloroethylamide; ALS, amyotrophic lateral sclerosis; Bcl-2, B cell lymphoma 2 protein; CHI, closed head injury; COX-2, cyclooxygenase-2; EAE, experimental autoimmune encephalomyelitis; Hsp70/72, heat shock protein 70/72; I/R, ischemia/reperfusion (injury); MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NOX, NADPH oxidase; TBI, traumatic brain injury; TNF-α, tumor necrosis factor alpha.

exerted neuroprotective effects through the attenuation of cerebral microcirculatory dysfunction and activation of microglial cells, with consequent proinflammatory response and oxidative/nitrative stress. Thus, CB2 receptor-driven signaling can indirectly attenuate ROS production and oxidative/nitrative (Figs. 6 and 7) stress following cerebral ischemia/reperfusion injury (249, 267, 280, 282, 289).

The neuroprotective effect of CBD has been evaluated in focal cerebral ischemia models as well. Hayakawa *et al.* have reported that the neuroprotective effect of THC is manifested mainly *via* the CB1 receptor and consequent temperature-dependent mechanisms, whereas the protective effects of CBD are independent of CB1 and of hypothermia (122). Moreover, CBD mitigated impaired cerebral microcirculation after reperfusion, inhibited myeloperoxidase (MPO) activity in neutrophils, (124), and inhibited high-mobility group box1 protein (HMGB1) expression and release from monocyte/macrophages, as well as glial activation induced by cerebral ischemia (123), suggesting a direct anti-inflammatory and an indirect antioxidant property of this plant-derived cannabinoid.

Traumatic brain injury

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality among young individuals with limited therapeutic options (21, 134). The acute brain damage presented after primary injury as the consequence of an external mechanical force results in contusion, laceration, and diffuse injuries. Secondary injury immediately presented after primary damage is accompanied with the activation of a complex cascade of molecular and cellular immune responses leading to neuroinflammation, excitotoxicity, oxidative/nitrative stress, and impaired calcium homeostasis, mitochondrial dysfunction, neuronal injury, and death. Moreover, post-traumatic changes in cognitive and neurological function might be presented as well [see review Refs. (58, 213, 309, 355)].

Inflammation has been shown to be a key player in TBI (355). Proinflammatory markers, including IL-1β, IL-6, and TNF-α, are released from activated astrocytes and/or microglial cells that engage leukocyte recruitment and exacerbate brain injury (Fig. 6). It has been also revealed that the extent of neuroinflammatory response in TBI closely correlates with the outcome (304, 349, 355). Recent findings also highlight that the repetitive head injury in athletes or in war veterans is associated with the development of brain atrophy, β- amyloid plaque formation, tau phosphorylation, and TDP-43 pathologies. All these events can contribute to the presence of clinical syndromes of cognitive impairment (35, 309).

Cannabinoids have been proposed to be neuroprotective against TBI. Previously, studies demonstrated that both AEA and 2-AG levels are increased in the brain following closed head injury (CHI) (304). Administration of exogenous 2-AG was able to attenuate CHI-induced neuropathology that was partially abolished by the administration of rimonabant. Moreover, 2-AG moderately improved neurological performance and attenuated edema formation when administered to $CB1^{-/-}$ mice subjected to CHI, suggesting that 2-AG-driven neuroprotection is not solely mediated *via* CB1 receptors (255). Exogenous 2-AG also decreased blood–brain barrier permeability and suppressed the acute expression of IL-1β, IL-6, and TNF-α and augmented the levels of endogenous antioxidants (256), indicating a unique role of 2-AG in TBI as an endogenous signaling mediator maintaining brain homeostasis against harmful insults (257, 358).

Along with these findings, it has been recently described that CB1 receptor expression decreases in the affected brain area after TBI and negatively correlates with edema formation and behavioral impairments (191). In contrast, an acute mitochondrial CB1 receptor upregulation has been documented after TBI proposing a dual role of mitochondrial CB1 signaling. First, it might aggravate metabolic defects and energy failure by inhibition of the mitochondrial cAMP-PKA signaling axis. Second, CB1 activation mitigates energy insufficiency by acting on the ATPase complex and attenuates neuronal apoptosis *via* activation of the mitochondrial protein kinase B (AKT) pathway (350).

Regarding CB2 receptor signaling, it should be noted that an increased CB2 receptor expression has been found after TBI that was associated with high neurological deficit, whereas no correlation with edema was noted (191). It is apparently due to activation of microglial cells that upregulate CB2 upon stimulation. Accordingly, activation of CB2 receptor signaling by using agonists 0–1966 and JWH-133 was shown to be neuroprotective in TBI by attenuating neuroinflammation *via* decreasing the mRNA level of iNOS in macrophage/microglia and reducing TNF-α level in the injured cortex, whereas pharmacological blockade or genetic deletion of the CB2 receptor worsened inflammation (6, 79). These findings support earlier observations that modulation of CB2 signaling decreases macrophage infiltration and microglial activation that might be an important target of further preclinical investigations (Figs. 6 and 7).

Along with the beneficial effect of CB2 receptor activation upon TBI, inhibition of the major 2-AG-metabolizing enzyme MAGL by using the inhibitor JZL-184 exerted neuroprotection *via* increasing brain 2-AG level and reducing the formation of proinflammatory prostaglandins in a repetitive mild CHI model (359). Additionally, TDP-43 aggregation and tau phosphorylation were also attenuated by MAGL inactivation.

Inhibition of FAAH by using the selective inhibitor PF-3845 has been shown to exert neuroprotection *via* increasing endogenous AEA level in mouse model of TBI (323). The authors revealed that chronic treatment with PF-3845 following TBI can reverse impairments in fine motor movement, memory, and anxiety-like behavior. In addition, it reduced neurodegeneration in the dentate gyrus and upregulated the expression of both B cell lymphoma 2 protein (Bcl-2) and heat shock protein 70/72 (Hsp70/72) in cortex and hippocampus, thereby improving cell survival in these areas. PF-3845 also suppressed the formation of amyloid precursor and the expression of iNOS and COX-2 (323).

With regard to human data, there are only few studies exploring the effect of cannabinoids (particularly CBD or THC) on neurological indices in patients with TBI. Nevertheless, according to recently published data assessing the effect of THC consumption on outcomes in TBI, a positive correlation has been observed between THC consumption and decreased mortality in adult patients with TBI (239).

In contrast, it has been also concluded by others that cannabis use might act as a neurological stressor and represent a risk factor following TBI in late adolescent and young individuals (278).

Taken together, neuroinflammation plays an important role in the propagation of neuronal damage following TBI. Therefore, reduction of proinflammatory processes, including microglial activation, blood–brain barrier dysfunction, leukocyte recruitment, and attenuation of oxidative/nitrative stress, might be an important therapeutic aim. Targeting CB2 signaling offers an alternative approach to improve these outcomes. In contrast, the exact role of CB1 receptor signaling in TBI needs to be further elucidated by utilizing rigorous temperature control.

Multiple sclerosis

Multiple sclerosis (MS) is an immune-mediated inflammatory disease causing randomly formed focal damage in the brain, affecting both the gray and white matter of the CNS. Increasing number of evidences highlight the role of the innate immune system in development and progression of MS [reviewed by Ref. (96)]. During the progression of MS, IFN-γ-secreting T helper 1 (Th1) cells and IL-17-secreting Th17 cells infiltrate the affected region of CNS, initiating microglial activation and local immune response that eventually lead to neuronal myelin sheath loss, impaired conductive properties, and axonal loss (62). Even though drugs targeting the immune system are capable of attenuating the progression of this disease in certain cases, there is no curative treatment for MS. Inflammatory plaques in MS patients show increased immunoreactivity for iNOS and nitrotyrosine (38, 131) associated with high levels of nitrate and nitrite in urine and serum (104, 105). The nitration of tyrosine residues in proteins of the blood–brain barrier and consequent dysfunction allow the further influx of inflammatory cells (64, 135).

Cannabinoids have a unique anti-inflammatory potential in the development and progression of MS (Tables 1 and 2). In the chronic phase of the disease, which is characterized by a profound neurodegeneration and hind limb spasticity in animal models, elevated AEA, palmitoylethanolamide (PEA), and 2-AG levels have been reported in response to neuronal damage (13, 14). Interestingly, spasticity was rapidly increased after administration of rimonabant, suggesting that alleviation of hind limb spasticity is CB1 dependent and can be a part of an endogenous compensatory mechanism mediated by the elevated level of endocannabinoids (53, 277). Accordingly, exogenous administration of AEA and 2-AG and N-acylethanolamine PEA has been shown to ameliorate the development of this disease in a mouse model of experimental MS (also known as experimental autoimmune encephalomyelitis [EAE]) (14, 53).

The rate of neurodegeneration in MS was decreased by the administration of CB1 receptor agonists (60). Consistently with this, CB1 receptor-deficient mice with EAE displayed more rapid neurodegeneration. These studies suggested that the neuroprotective role of CB1 signaling may be manifested *via* the inhibition of glutamate-induced excitotoxicity and oxidative stress (203, 277), which are important contributors to the course of neurodegeneration in MS (274).

Recent studies also showed that the CB2 receptor agonist, JWH-133, ameliorated tremor and spasticity in EAE mice (13). Similarly, treatment with another CB2 agonist, HU-308, attenuated the development of EAE in mice (301). In the latter study, CB2 receptor activation promoted autophagy in the spinal cord of EAE mice and inhibited the expression and activation of NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome in BV2 microglia cell line *in vitro* (301). Consistently with these observations, $CB2^{-/-}$ mice displayed greater vulnerability to neurofilament degeneration, inflammation, apoptosis, and axonal damage in EAE mice similarly to CB1-deficient mice (150, 254, 294).

Additionally, a protective effect of the MAGL inhibitor, JZL184, was documented in cultured oligodendrocytes as well as in EAE mice. JZL-184 suppressed cell death by mild activation of AMPA receptors in oligodendrocytes *in vitro* and preserved the integrity of myelin sheath and suppressed microglial activation *in vivo* (26). This effect was imitated by the administration of 2-AG and by AEA in a concentration-dependent manner. Interestingly, inhibition of the AEA-metabolizing enzyme FAAH with URB597 was ineffective in attenuating oligodendrocyte cell death. The authors concluded that oligodendrocyte protection from excitotoxicity of MAGL blockade results in the reduction of AMPA-induced cytosolic calcium overload, mitochondrial membrane depolarization, and production of ROS (26). It should be also noted that chronic MAGL inhibition is associated with downregulation/desensitization of brain CB1 receptors (298), thus the role of MAGL in the context of MS needs to be further elucidated.

As for the nonpsychoactive natural cannabinoids, it has been shown that CBD ameliorated clinical signs of EAE that was accompanied by diminished axonal damage and inflammation, microglial activation, and T cell recruitment (174). However, a recent finding indicates that coadministration of PEA with CBD was not as effective in EAE compared with each drug administered alone, indicating that there is an antagonistic interaction between CBD and PEA in protection against EAE (279). THC has also been shown to diminish the progression of MS in EAE by attenuating the inflammatory process, which appears to be CB1 dependent (93). Similarly, the beneficial effect of the nonpsychotropic synthetic cannabinoid dexanabinol (HU-211) was also evaluated on EAE (1). The authors reported a reduction in the inflammatory response in the brain and spinal cord in EAE mouse treated with HU-211.

The abovementioned results encouraged clinicians to test the feasibility of THC/CBD in reduction of the rate of neurological damage and refractory spasticity both in acute and chronic phases of MS (89, 192, 300). However, the results of these clinical trials were inconsistent, and clearly more investigations are required with greater sample size to evaluate whether cannabinoids can lower the progression of this disease.

Collectively, diminution of inflammation during the course of MS is an important therapeutic approach. Drugs inhibiting TNF-α release, reducing edema, free radical production, and improving blood–brain barrier integrity might be useful therapeutically to slow down the rate of disease progression in MS.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) is a progressive neurodegenerative disorder that primarily affects motor neurons in the spinal cord, brainstem, and cortex, leading to muscle weakness, paralysis of respiratory muscles, and eventually death. The majority of ALS is thought to be sporadic; however, about 10% of all cases have familial origin. The major histologic sign of ALS is the formation of inclusion bodies in certain brain regions, which comprise apoptotic neurons and the surrounding activated astrocytes.

As for the genetic background of ALS, two major factors have been identified playing a pivotal role in the development

of this disease: an inherited autosomal mutation of the superoxide dismutase-1 (SOD-1)-encoding gene leading to impaired neuronal antioxidant capacity (291). Additionally, an expansion of a hexanucleotide sequence in the noncoding region of the *C9ORF72* gene has been shown to be associated with ALS (286). Notably, other genes might be involved in the progress of this form of neurodegeneration (170). Numerous mechanisms have been implicated in the pathogenesis of ALS, including neurofilament accumulation, dysregulation of axonal transport, glutamate-mediated excitotoxicity, neuroinflammation and consequent microglial activation, and oxidative stress (29, 284, 318, 363) (Figs. 6 and 7). However, neither of these mechanisms has been identified to be the major cause of ALS.

Elevated levels of AEA and 2-AG have been documented in transgenic G93A-SOD1 mice that can recapitulate several features of ALS. Witting and her coworkers suggested that the increase in endocannabinoid levels in G93A-SOD1 mice might be a part of an endogenous defense mechanism, which is mediated *via* the AEA-CB1 receptor signaling axis (347). Similarly, Bilsland *et al.* have reported that genetic ablation of FAAH in these G93A-SOD1 mice and the consequent increase of AEA level significantly lowered the progression of ALS (28, 29). Moreover, WIN 55,212-2 treatment of G93A-SOD1 mice reduced the clinical signs of the disease; however, either FAAH ablation or treatment with the nonselective cannabinoid receptor agonist WIN 55,212-2 had no effect on life span of G93A-SOD1 mice compared with controls (28). These results suggest a neuroprotective role of cannabinoids in ALS that is not exclusively mediated *via* CB1 receptor and may involve CB2 receptor signaling.

Rossi and his coworkers have demonstrated an altered sensitivity of cannabinoid CB1 receptors controlling both glutamate and GABA transmission in the striatum of G93A-SOD1 mice, suggesting that adaptation of the ECS might be involved in the pathophysiology of ALS (293).

The protective effect of specific CB2 receptor agonists has been evaluated in ALS as well. Notably, CB2 receptors existing primarily in the periphery are dramatically upregulated in the affected areas, likely due to the activation of microglial cells (303, 328, 347). It has been recently reported that daily administration of CB2 agonist AM-1241 to G93A-SOD1 mice at the onset of clinical signs can increase the survival upon disease onset and improve the outcome (303), suggesting that CB2 agonists might attenuate local inflammation, motor neuron degeneration, and preserve motor function.

Moreno-Martet *et al.* have conducted a study with a Sativex®-like combination of phytocannabinoids (THC and CBD-enriched plant extract) in G93A-SOD1 mice (224). Even though the treatment preserved motor neurons in the spinal cord of SOD-1 mutant mice, it failed to preserve the integrity of neuromuscular junctions, achieving only poor neurological recovery. On the other hand, a marked upregulation of CB2 receptors was demonstrated in G93A-SOD1 mice; however, other genes involved in endocannabinoid metabolism and signaling were unchanged. Importantly, there were no changes in animal survival (224).

In spite of the increasing number of preclinical studies, there are only relatively few clinical trials evaluating the effect of THC/CBD in humans with ALS (7, 343). People with ALS have reported that cannabis consumption can alleviate some of their symptoms, including pain, muscle spasms, depression, and excessive production of saliva (7). However, there are no convincing clinical data so far investigating the benefits of plant-derived cannabinoids in ALS.

Taken together, ROS produced in motor neurons in response to excitotoxic activation can induce an oxidative disruption of glutamate transport in surrounding astrocytes, leading to the expansion of excitotoxic stress that can trigger the progression of ALS (284, 285). CB1 receptor stimulation was shown to block TNF-α-induced upregulation of AMPA glutamate receptors and exerted protection from excitotoxic death in hippocampal neuron cultures (364). Mitochondrial abnormalities have been found to play a critical role in the development of ALS, amplifying ROS production (169, 348). Therefore, it is conceivable that drugs targeting CB1 receptor signaling might limit the extent of oxidative damage in motor neurons associated with glutamate receptor hyperstimulation; however, the direct link between ROS-induced neuronal death and endocannabinoids needs to be elucidated in this disease. On the other hand, targeting CB2 signaling by selective receptor agonist may indirectly reduce oxidative/nitrative stress in ALS by attenuating microglial activation, inflammatory response, and subsequent oxidative stress.

Parkinson's disease

Oxidative/nitrative stress has been shown to increase in neurons with age due to their postmitotic character, which may also result in neuronal damage, dysfunction, and cell death. Accordingly, an ROS-dependent impairment of neuronal function can be observed in Parkinson's disease as the most common form of synucleinopathy (103).

Postmortem analysis of human brain samples with Parkinson's disease showed an augmented ROS production in the affected regions. Peroxynitrite-mediated nitration of certain tyrosine residues in the neuronal presynaptic protein α-synuclein has been shown to alter its folding, resulting in protein dysfunction, impaired protein degradation, and subsequent formation of Lewy bodies. Peroxynitrite further contributes to the progression of Parkinson's disease through nitration of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of dopamine, causing progressive nigrostriatal dopaminergic neuron loss resulting in motor disturbances and cognitive impairment (31, 103, 176, 312). Moreover, certain tyrosine residues determine the substrate specificity of monoamino oxidase B (MAO B). Thus, nitration of these tyrosine residues also leads to altered dopamine metabolism (102).

Furthermore, peroxynitrite is known to be involved in reduction of the intracellular glutathione level in substantia nigra by inactivating glutathione reductase (27). As early events in parkinsonism, dysfunctional glutathione reductase and the impaired function of mitochondrial complex I exacerbate oxidative stress, leading to neuronal cell death (235).

Since oxidative/nitrative stress is a hallmark of parkinsonism, the possible role of cannabinoids has been investigated in this pathophysiological condition as well (Tables 2 and 3). The effect of targeted activation of CB1 receptors in parkinsonism remains controversial in the literature. García-Arencibia *et al.* have reported that daily administration of selective CB1 receptor agonist, ACEA, or the nonselective cannabinoid receptor agonist, WIN 55,212-2, failed to reverse 6-hydroxydopamine-induced dopamine depletion in the affected region (97). In

contrast, another study has concluded that activation of CB1 receptor-mediated signaling contributed to enhanced survival of nigrostriatal dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of Parkinson's disease (54). This protective effect was accompanied by suppression of NOX enzymes, decreased ROS production, and reduced expression and release of proinflammatory cytokines originating from activated microglia. Nevertheless, activation of CB1 receptor might have disadvantages in parkinsonism since the hypokinetic effect of CB1 activation might worsen the symptoms of Parkinson's disease such as bradykinesia. In contrast, inhibition of CB1-mediated signaling attenuated Parkinson's disease-associated akinesia (85).

Interestingly, the specific FAAH inhibitor, URB597, has been found to be protective in probenecid and MPTP-induced experimental parkinsonism (47). URB597 prevented MPTP-induced motor impairment, but it failed to preserve dopamine levels in the substantia nigra or regulate glial cell activation. The symptomatic relief of URB597 was also studied in haloperidol-induced catalepsy assays, whereas the anticataleptic effect of URB597 was abolished by either pharmacological blockade or genetic ablation of CB1 and CB2 receptors, suggesting a pivotal role of FAAH inhibition and concomitant AEA increase in the motor symptoms of Parkinson's disease. However, the role of CB2 receptor in symptomatic relief should be uncovered.

Similarly, it was shown that the nonselective cannabinoid receptor agonist WIN 55,212-2 protected against nigrostriatal neuron loss in mouse model of MPTP-induced neurotoxicity and neuroinflammation. The neuroprotective effect of WIN 55,212-2 was associated with elevated dopamine and 3,4-dihydroxyphenylacetic acid levels in the substantia nigra pars compacta and dorsal striatum. In addition, the authors have documented significant microglial activation and concomitant upregulation of CB2 receptors in the ventral midbrain. On the other hand, treatment with the CB2 receptor agonist JWH015 attenuated MPTP-induced microglial activation, whereas genetic ablation of CB2 receptors aggravated neuronal death (276).

Neuroprotective effect of the MAGL inhibitor JZL-184 was also assessed in the dopaminergic-like SH-SY5Y cell line exposed to 1-methyl-4-phenylpyridinium iodide (MPP^+) toxicity (11). The protective effect of JZL-184 on cell survival was abolished by the CB2 receptor antagonist AM630 and it was mimicked by the CB2 receptor agonist JWH133. Additionally, rimonabant, a CB1 receptor inverse agonist/antagonist, did not affect JZL-184-induced cell survival. Thus, MAGL inhibition provides further evidence for the beneficial effects of CB2 signaling in an *in vitro* model of Parkinson's disease.

Studies investigating the effect of plant-derived CBD revealed that CBD is able to attenuate mitochondrial dysfunction and oxidative damage and upregulate the mRNA level of enzymes in endogenous defenses against oxidative stress in experimental models of Parkinson's disease (97, 99, 184).

To date, there are no clinical data addressing the neuroprotective effects of cannabinoids and assessing the effects of THC and/or CBD in patients with Parkinson's disease. Clinical studies mainly focus on the relief of specific symptoms, including bradykinesia, tremor, and levodopa-induced dyskinesia (91, 92, 215); however, preclinical findings support the concept that an effective therapy against Parkinson's disease should aim to improve antioxidant capacity. Control of inflammatory response by CB2 receptor activation and inter-related oxidative/nitrative stress might be beneficial, and the blockade of CB1 receptor signaling could reduce motor inhibition. However, the exact role of CB1 receptor signaling in parkinsonism needs to be better understood.

Alzheimer's disease

Alzheimer's disease is characterized by progressive neurodegeneration due to the formation of β-amyloid plaques, neurofibrillary tangles, gliosis, and neuroinflammatory response (Fig. 6). All these effects lead to loss of cognitive function (344). Interestingly, oxidative stress has been shown to be an early event in the progression of neurodegeneration associated with Alzheimer's disease (41, 136, 216, 223). Increased expression of nNOS has been documented in astrocytes surrounding β-amyloid plaques in human subjects (307). An elevated iNOS and eNOS expression in neurofibrillary tangles has also been reported by other groups, suggesting that enhanced production of NO by reactive astrocytes and formation of peroxynitrite play a pivotal role in the pathogenesis of Alzheimer's disease (65, 193, 194). Protein nitration is increased in the cortex, neocortex, or in hippocampus in human subjects suffering from Alzheimer's disease (43, 129), coupled with decreased antioxidant capacity and reduced superoxide dismutase, catalase, and glutathione peroxidase activity in the affected brain regions (258, 354).

The relationship between Alzheimer's disease and the cannabinoid system has been extensively investigated (Tables 1 and 2). Several studies revealed that β-amyloid-induced progressive hippocampal neurodegeneration is associated with increased 2-AG, but not AEA, production *in vivo* (5, 87, 333). Controversially, augmented FAAH activity has been confirmed in astrocytes associated with senile plaques that lead to increased generation of arachidonic acid, aggravating inflammatory stimuli (24, 63).

Increased CB1 expression has been shown at earlier stages of Alzheimer's disease in hippocampal regions and internal layers of frontal cortex, which was decreased at the advanced stage of disease.

Elevation of 2-AG and modulation of CB2 receptor signaling either by using specific CB2 agonists (151, 170) or by inhibiting 2-AG-degrading enzyme MAGL might result in reduced microglial activation, decreased inflammatory response, attenuated oxidative stress, and attenuated β-amyloid plaque accumulation in the affected brain areas (49, 272). Notably, MAGL inhibition has been reported to prevent neuroinflammation, decrease neurodegeneration and maintain the integrity of hippocampal synaptic structure and function, and improve long-term synaptic plasticity, thereby supporting spatial learning and attenuating memory impairments in animals with Alzheimer's disease (49) (Figs. 6 and 7).

The nonpsychoactive phytocannabinoid, CBD, has been demonstrated to be neuroprotective *in vitro* and *in vivo* in Alzheimer's disease models (146). Neuronal cells pretreated with CBD showed diminished iNOS expression and reduced hyperphosphorylation of tau protein following Aβ treatment (83). Moreover, ROS levels, lipid peroxidation products, and caspase-3 activation were also attenuated by CBD (147). Similarly, mice treated with CBD before Aβ exposure also displayed an impaired iNOS and IL-1β protein expression and reduced NO and IL-1 β release (84).

Moreover, CBD dose-dependently decreased glial fibrillary acidic protein (GFAP) expression, suggesting attenuated microglial activation and neuroinflammation. However, the protection of CBD in neuronal cells cannot be fully attributed to its antioxidant properties; further clarification of its pharmacology is required to explain the mechanism of action (299).

In spite of the numerous promising results with cannabinoids in preclinical models of Alzheimer's disease, suitable clinical studies are still lacking in patients suffering from Alzheimer's disease. Clinical studies conducted so far have focused on the symptom-relieving effects of cannabinoids (dronabinol, CBD); however, they did not investigate the effect of cannabinoids on the progression of this devastating disease (339). Since oxidative/nitrative stress and NO production by active astrocytes and microglial cells in neurofibrillary tangles are the hallmarks of Alzheimer's disease even at early phases, therapies targeting ROS production might hold great therapeutic potential in slowing progression of the disease.

Huntington's disease

Huntington's disease is a dominantly inherited, progressive, autosomal neuropsychiatric disorder. The prevalence of Huntington's disease is lower than the other abovementioned neurodegenerative complications. It is characterized by a progressive neurodegeneration in the basal ganglia and certain cortical regions ultimately leading to the presence of involuntary movements, dystonia, psychiatric symptoms, and dementia (8, 100). The massive neuronal damage and cell loss are caused by an expansion of a trinucleotide (CAG) repeat encoding glutamine in the gene of huntingtin. This polyglutamine extension of huntingtin leads to conformational changes and abnormal protein–protein interactions.

Moreover, mutant huntingtin can bind to certain transcription factors resulting in a decreased expression of specific genes that might be crucial in neuronal survival (100). Substantial evidence also suggests an important role of oxidative stress and excessive production of NO in the development and progression of Huntington's disease (42). Increased iNOS expression, enhanced $ONOO^-$ generation, and elevated 3-nitrotyrosine (3-NT) formation have been shown in neuronal, glial, and vascular cells of diseased human brains as well as in animal models of Huntington's disease (48, 95, 112, 266). To date, there is no curative treatment for Huntington's disease, and only palliative care is available to reduce motor neuronal disturbances, chorea, and dystonia.

A decreased expression of CB1 receptors has been documented in the subset of neurons of the lateral striatum, cortex, and hippocampus before the clinical onset of Huntington's disease, suggesting involvement of the cannabinoid system in the development of this neurodegenerative disorder (19, 68, 106, 180, 334). Furthermore, mutant huntingtin has been suggested to play a unique role in the depletion of CB1 receptors by silencing CB1 transcription at the level of gene expression (182). Moreover, loss of CB1 function has been shown to contribute to cognitive, behavioral, and motor deficits in animal models of Huntington's disease (33, 34). Accordingly, targeting CB1 receptors located on cortical glutamatergic neurons that project to the striatum attenuated neuronal loss rather than the CB1-mediated silencing of GABAergic striatal neurons underlining the importance of different subsets of CB1-expressing neurons in the pathology of Huntington's disease (51).

In addition, it has been recently shown that compounds acting selectively on CB2 receptors are able to attenuate the progression of Huntington's disease by ameliorating inflammation and microglial activation in striatum following malonate-induced damage (295). The authors also documented that activation of CB2 receptors significantly reduced the levels of proinflammatory TNF-α, which was elevated in the malonate-induced lesion. In addition, mice deficient in CB2 receptor were more sensitive to malonate-induced striatal cell loss compared with wild-type animals (295). Accordingly, in another animal model of Huntington's disease, induction of striatal excitotoxicity by quinolinic acid administration exacerbated brain edema, microglial activation, proinflammatory mediator release, and neuron degeneration. All these effects were more severe in CB2 receptor-deficient mice and were attenuated by administration of the selective CB2 receptor agonist HU-308 to wild-type mice (295).

The nonspecific DAGL inhibitor O-3841 and the specific MAGL inhibitor JZL-184 were also tested in a malonate-induced striatal damage model (331). Surprisingly, the inhibition of 2-AG biosynthesis by using the nonspecific DAGL inhibitor O-3841 was neuroprotective following striatal malonate treatment due to the attenuation of overproduction of the neuroinflammatory prostaglandin E2 glyceryl ester (PGE2-G), formed by COX-2-mediated oxygenation of 2-AG. Accordingly, MAGL inhibition by JZL-184 or the administration of PGE2-G exacerbated the malonate-induced striatal damage (331).

The neuroprotective effect of CBD has been also evaluated in animal models of Huntington's disease. CBD exerted neuroprotection when striatal atrophy was induced by the mitochondrial toxin 3-nitropropionic acid (3-NP) (296). 3-NP-induced neuronal loss mimics mitochondrial defects with the subsequent generation of ROS in patients suffering from Huntington's disease. This protection was independent from cannabinoid receptor activation and presumably caused by the antioxidant nature of CBD. The neuroprotective potential of THC has been also evaluated in rats with striatal degeneration induced by malonate (183). Administration of THC increased malonate-induced striatal cell loss compared with vehicle. Surprisingly, rimonabant also enhanced malonate-induced neuronal damage in a greater extent, suggesting complex overlapping mechanism in the pathology of Huntington's disease (183).

The effects of cannabinoids have been also studied in patients with Huntington's disease, although these clinical trials evaluated only the alleviation of specific symptoms, such as chorea and behavioral disturbances [reviewed by Ref. (86)], and were not conclusive. Clearly, further studies are required to assess the role of interaction of cannabinoids and ROS production in the disease progression.

Conclusions

Endocannabinoid production may be triggered during tissue injury by oxidative stress and inflammation. In turn, endocannabinoids may also control oxidative stress by directly or indirectly modulating CB1 and CB2 signaling or CB receptor-independent processes (*e.g.,* COX-2-dependent eicosanoid pathways). Consequently, this may lead to either tissue-protective or damaging effects depending on the injury and cell/tissue type and/or context. Better understanding of these complex interactions and tissue-specific differences may lead to better cannabinoid-based therapies in the future.

For the moment, it appears that targeting CB2 signaling with selective agonists in various neuroinflammatory/neurodegenerative diseases may represent a promising therapeutic avenue to attenuate inflammation and inter-related oxidative/nitrative stress if the impending target validation studies and studies with novel ligands are successful. Certain cannabis-based natural constituents, such as cannabidiol, may also have therapeutic potential to treat certain human diseases associated with oxidative stress and inflammation. Tables 1–3 summarize the most commonly used cannabinoid ligands (Table 1), evidence on the interplay of endocannabinoids and oxidative stress (Table 2), and implication of targeting the ECS in oxidative stress-related neurodegenerative diseases (Table 3).

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Abbreviations Used

2-AG = 2-arachidonoyl glycerol
3-NP = 3-nitropropionic acid
3-NT = 3-nitrotyrosine
4-HNE = 4-hydroxynonenal
6-OHDA = 6-hydroxydopamine
8-iso-$PGF_{2\alpha}$ = 8-iso-prostaglandin $F_{2\alpha}$
Abhd12 = α/β-hydrolase 12
Abhd4 = α/β-hydrolase 4
Abhd6 = α/β-hydrolase 6
ACEA = arachidonoyl-2-chloroethylamide
AEA = anandamide
AKT = protein kinase B
ALS = amyotrophic lateral sclerosis
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AT1 receptor = angiotensin II receptor type 1
ATP = adenosine triphosphate
Bcl-2 = B cell lymphoma 2 protein
cAMP = cyclic adenosine monophosphate
CB1 = cannabinoid 1 receptor
CB2 = cannabinoid 2 receptor
CBD = cannabidiol
CCLs = C-C motif chemokines
cGMP = cyclic guanosine monophosphate
CHI = closed head injury
CNS = central nervous system
COXs = cyclooxygenases (also known as prostaglandin-endoperoxide synthases)
COX-2 = cyclooxygenase-2
CXCLs = C-X-C motif chemokines
CYP 450 = microsomal cytochrome P450 enzymes
DAG = diacylglycerol
DAGLα = diacylglycerol lipase α
DAGLβ = diacylglycerol lipase β
DAMPs = damage-associated molecular patterns
DNA = deoxyribonucleic acid
EAE = experimental autoimmune encephalomyelitis
ECS = endocannabinoid system
EET = epoxyeicosatrienoic acids
EET-EAs = epoxyeicosatrienoic ethanolamines
EET-Gs = epoxyeicosatrienoic glycerols
eNOS (NOS3) = endothelial nitric oxide synthase
ER = endoplasmic reticulum
ERK = extracellular signal-regulated kinases
FAAH = fatty acid amide hydrolase
GFAP = glial fibrillary acidic protein
GPR119 = G protein-coupled receptor 119
GPR55 = G protein-coupled receptor 55
H_2O_2 = hydrogen peroxide
HETE-EAs = hydroxyeicosatetraenoic ethanolamines
HETE-Gs = hydroxyeicosatetraenoic glycerols
HETEs = hydroxyeicosatetraenoic acids
HIF-1 = hypoxia-inducible factor 1
Hsp70/72 = heat shock protein 70/72
ICAM-1 = intercellular adhesion molecule 1
IFN-γ = interferon-γ
IL-1β = interleukin 1β
IL-6 = interleukin 6
IL-10 = interleukin 10
IL-17 = interleukin 17
iNOS (NOS2) = inducible nitric oxide synthase
JNKs = c-Jun N-terminal kinases
LPS = lipopolysaccharide
lyso-PLD = lysophospholipase D
MAGL = monoacylglycerol lipase
MAO B = monoamino oxidase B
MAPK = mitogen-activated protein kinase
MPO = myeloperoxidase
MPP^+ = 1-methyl-4-phenylpyridinium iodide
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mRNA = messenger ribonucleic acid
MS = multiple sclerosis
NAD^+ = nicotinamide adenine dinucleotide
NADA = N-arachidonoyl dopamine
NADPH = nicotinamide adenine dinucleotide phosphate (reduced form)
NAPE = N-acylphosphatidylethanolamine
NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3 = NACHT, LRR, and PYD domain-containing protein 3 (also known as cryopyrin)
NMDA receptor = *N*-methyl-D-aspartate receptor
nNOS (NOS1) = neuronal nitric oxide synthase
NO = nitric oxide
NOS = nitric oxide synthase
NOXs = NADPH oxidases
$O_2\bullet^-$ = superoxide
OH• = hydroxyl radical
$ONOO^-$ = peroxynitrite
PARP-1 = poly(APD-ribose) polymerase-1
PEA = palmitoylethanolamide
PGE_2 = prostaglandin E_2
PGE2-G = prostaglandin E2 glyceryl ester
PKA = protein kinase A
$PLA_2\gamma$ = calcium-independent phospholipase A2γ
PLC = phospholipase C
PLD = phospholipase D
PPARs = peroxisome proliferator-activated receptors
PTPN22 = protein tyrosine phosphatase, nonreceptor type 22
RNS = reactive nitrogen species
ROS = reactive oxygen species
SOD-1 = superoxide dismutase-1
STAT3 = signal transducer and activator of transcription 3
TBI = traumatic brain injury
Th1 cells = T helper 1 cells
Th17 cells = T helper 17 (IL-17-secreting) cells
THC = Δ^9-tetrahydrocannabinol
THCV = Δ^9-Tetrahydrocannabivarin
TNF-α = tumor necrosis factor alpha
TRPV1 = transient receptor potential vanilloid type 1
VCAM-1 = vascular cell adhesion molecule 1
VSMCs = vascular smooth muscle cells