

## Review Article

# Update on the Role of Cannabinoid Receptors after Ischemic Stroke

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Cannabinoids are considered as key mediators in the pathophysiology of inflammatory diseases, including atherosclerosis. In particular, they have been shown to reduce the ischemic injury after acute cardiovascular events, such as acute myocardial infarction and ischemic stroke. These protective and anti-inflammatory properties on peripheral tissues and circulating inflammatory have been demonstrated to involve their binding with both selective cannabinoid type 1 (CB<sub>1</sub>) and type 2 (CB<sub>2</sub>) transmembrane receptors. On the other hands, the recent discoveries of novel different classes of cannabinoids and receptors have increased the complexity of this system in atherosclerosis. Although only preliminary data have been reported on the activities of novel cannabinoid receptors, several studies have already investigated the role of CB<sub>1</sub> and CB<sub>2</sub> receptors in ischemic stroke. While CB<sub>1</sub> receptor activation has been shown to directly reduce atherosclerotic plaque inflammation, controversial data have been shown on neurotransmission and neuroprotection after stroke. Given its potent anti-inflammatory activities on circulating leukocytes, the CB<sub>2</sub> activation has been proven to produce protective effects against acute poststroke inflammation. In this paper, we will update evidence on different cannabinoid-triggered avenues to reduce inflammation and neuronal injury in acute ischemic stroke.

## 1. Introduction

Ischemic stroke has become one of the leading causes of mortality and severe disability in several countries, including developing nations [1, 2]. It is provoked by an acute, complete, and prolonged interruption of the arterial flow in the brain characterized by residual tissue infarction [3]. Although extensive studies have been performed to investigate the role of different factors influencing stroke sequelae, the disease pathophysiology remains largely unclear. Physical steps of the ischemic event (such as the transient or permanent interruption of the blood flow and the focal or

global cerebral ischemia) are clearly pivotal determinants for the disease prognosis. However, these aspects do not explain some spatial heterogeneity in the cellular damage that might directly reflect neuronal intrinsic susceptibility to injury [4, 5]. Since cannabinoids might accumulate in the ischemic brain [6, 7] and bind their receptors in neurons [8], promising neuroprotective strategies targeting this system to reduce the neuronal ischemic injury have been investigated. On the other hand, since cannabinoids have been shown to modulate brain resident microglial cells [9, 10], cerebral blood vessels [11–14], and circulating inflammatory cells [15, 16], a second therapeutic approach targeting

postischemic inflammation has been also explored. In the following paragraphs, we will update scientific results on the role of the cannabinoid receptors as potential regulators of both nervous and immune systems after ischemic stroke [9, 17, 18].

## 2. Cannabinoids and Their Receptors

Endogenous cannabinoids (endocannabinoids) are chemically amides and esters of long polyunsaturated fatty acids including arachidonylethanolamide (anandamide [AEA]) and 2-arachidonoylglycerol (2-AG). AEA is a minor constituent of the N-acylethanolamines (NAEs) family and has been found elevated in serum and plaques of patients with severe atherosclerotic diseases [19, 20]. On the other hand, 2-AG has been shown to reach higher concentrations than anandamide analogues (such as palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in the brain and atherosclerotic vessels [21]. Synthetic cannabinoids have been also investigated in animal models showing an improvement of the ischemic injury in the liver, heart, and brain [22–24]. Furthermore, phytocannabinoids have been also isolated from the *Cannabis sativa*. Since this plant contains about 80 different cannabinoids, a strong work is still needed to test all these active compounds. This delay in cannabinoid research might be also due to the very low dose of certain cannabinoids in the plant. Thus, since  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) represent up to 40% of the total cannabinoid mass [25], these compounds have been considered as the most active mediators.

The effects of cannabinoids are classically attributed to the activation of the two major cannabinoid receptors (the cannabinoid receptors type 1 [CB<sub>1</sub>] and type 2 [CB<sub>2</sub>]). These transmembrane receptors are pivotal components of the physiological endocannabinoid system together with endogenous cannabinoids (endocannabinoids), their transporters, and synthetic/degrading enzymes [26]. CB<sub>1</sub> is highly expressed in the brain [27–31] as well as in cardiovascular tissues including the heart [32–34] and vascular vessels [35–38]. Although it has been recently shown in the brain [39, 40], CB<sub>2</sub> is mainly expressed in the immune and hematopoietic cells [10, 41–43]. Importantly, novel receptors capable of binding cannabinoids have been recently identified. In particular, the transient receptor potential vanilloid (TRPV) channels might be activated by cannabinoids [44–46]. Among these channels, the activity and expression of TRPV type 1, 3, and 4 could be modulated by classical cannabinoid receptors agonists [41, 47–52]. On the other hand, there is growing evidence that cannabinoids can activate the peroxisome proliferator-activated receptors (PPAR, a family of nuclear receptors) in neurological diseases [53–57]. Although its activity has not been clarified yet, the orphan receptor GPR55 has been also identified to potentially bind cannabinoids and intracellularly transduce their signals [58, 59].

## 3. Role of Cannabinoid Receptors in Poststroke Inflammatory Injury

Some key events in the pathophysiology of ischemic stroke include increased levels of inflammatory cytokines in the brain, activation of microglia, and adhesion and migration of peripheral leukocytes as a result of damage to the blood-brain barrier [60]. A severe immunosuppression also characterized by spleen atrophy has been described to follow this initial inflammatory burst [61]. In order to inhibit the acute inflammatory phase (strongly associated with cerebral injury) [62], the treatment with  $\Delta^9$ -tetrahydrocannabinol (THC, a cannabinoid receptor agonist) has been shown to induce immunomodulatory properties *in vitro* [63–65]. Endocannabinoids (such as AEA and 2-AG) might be also released by immune cells and neurons, thus locally modulating immune response and cell differentiation within the brain [66, 67]. Several immune cells (such as lymphocytes, monocytes, and neutrophils, capable of infiltrating the injured brain) have been shown to express on their surface membrane both CB<sub>1</sub> and CB<sub>2</sub> receptors [41, 47, 68–71]. CB<sub>1</sub> receptor is particularly expressed on T lymphocytes and might be further upregulated by cannabinoid stimulation [69, 72–75]. This mechanism might favor the paracrine protective activity of AEA, which is highly produced in the ischemic brain area and locally inhibits T lymphocyte proliferation [76]. Importantly, CB<sub>1</sub> expression has been also confirmed on cerebral macrophage-like cells, suggesting a potential direct effects of cannabinoids also on populations resident in the brain [77]. On the other hand, the majority of beneficial effects of cannabinoids is associated with CB<sub>2</sub> receptor activation, which is classically described to inhibit immune proinflammatory functions. CB<sub>2</sub> receptor is also expressed in immune organs (such as thymus and spleen) [78] and circulating inflammatory cells (including T-, B-lymphocytes, NK cells and monocytes and neutrophils) [79–81]. Importantly, CB<sub>2</sub> protein has been recently detected in astrocytes [82], microglia [83], neural subpopulations, and oligodendroglial progenitors [84], suggesting a potential direct regulation of CB<sub>2</sub> in cerebral poststroke inflammation also in brain inflammatory cells [85]. The levels of CB<sub>2</sub> receptor on microglial cells might depend on the cell activation state in response to infection, inflammation and stress [66, 86]. CB<sub>2</sub> receptor is also upregulated in restricted areas of the spinal cord in response to peripheral nerve injury [87], suggesting that neurons and resident inflammatory cells might benefit of cannabinoid treatments. Since CB<sub>1</sub> and CB<sub>2</sub> surface expression is upregulated during the inflammatory activation [66, 88–90], treatment with cannabinoids might be even more effective in the early post-ischemic phase. Treatment with the selective CB<sub>2</sub> agonist JWH-133 was shown to significantly reduce microglial activation and inflammatory gene expression (such as interleukin [IL]-6, tumor necrosis factor [TNF]- $\alpha$ , regulated on activation, normal T-cell expressed and secreted [RANTES], monocyte chemoattractant protein [MCP]-1, and macrophage inflammatory peptide [MIP]-1 $\alpha$ ) in a mouse model of permanent middle cerebral artery occlusion and focal cerebral ischemia [91]. Importantly, this potent anti-inflammatory activity

was accompanied by the JWH-133-mediated improvement of brain infarction and neurological “clinical” outcomes [91]. Accordingly, pretreatment with CB<sub>2</sub> agonists has been shown to attenuate the poststroke enhancement of leukocyte/endothelial cells interaction, adhesion molecule expression, and disruption of blood-brain barrier (BBB) [92–94]. In addition, CB<sub>2</sub> knockout mice developed an increased cerebral infarction, accompanied by worsened neurological functions when compared to wild-type mice [92].

Confirming recent studies in other macrophage-mediated inflammatory diseases (such as atherosclerosis and rheumatoid arthritis) [15, 18, 95], these studies clearly show that CB<sub>2</sub> activation might actively reduce the post-stroke cerebral microglial inflammation.

Cannabinoids might also affect T lymphocyte function and survival [65]. Although the role of T lymphocytes in post-stroke inflammation has not been clarified yet in human beings [96, 97], recent evidence from mouse models indicated that these cells might modulate their functional capacities after an acute cerebral ischemia [61, 62, 98, 99]. In particular, the CD4+CD25+ regulatory T cells have been suggested to play cerebroprotective activities in mice after a focal cerebral ischemia [62, 98]. Therefore, the cannabinoid-mediated benefits might involve the T lymphocyte response. In other inflammatory diseases, cannabinoid agonism has been shown to affect proliferation, polarization [66, 100], and cytolytic capacity [101] of T cells. Recently, Tanikawa and coworkers published that treatment with WIN-55,212-2 favors the lymphocyte migration within the spleen, supporting that this cannabinoid agonist directly downregulates the immune response [102]. Accordingly, 2-AG strongly reduces mitogen-induced proliferation of mouse splenocytes [103]. These studies support a potential therapeutic role of cannabinoid agonists to reduce T lymphocyte-mediated inflammation in the post-stroke acute phase.

Although some effort has been made in the past decades to clarify the role of the cannabinoid system in post-stroke inflammation, discrepancies deriving from the use of different types and doses of cannabinoids in both *in vivo* and *in vitro* models still exist and represent a major limitation to define clear conclusions.

#### 4. The Cannabinoid System in the Ischemic Neuronal Injury

The acute reduction of blood flow with the consequent abrogation of oxygen and nutrient supply in the peripheral cerebral tissue has been shown to significantly modify the neural electrolytic equilibrium and metabolism. The cytosolic increase of reactive oxygen species (ROS), calcium, and sodium has been described to directly increase neuron necrosis and apoptosis in the early hours after the ischemic onset [104]. Normally, the burst of ROS in the cytosol is accompanied by a reduction in pH, while the release of glutamate from the core of the infarcted area increases the permanency of high intracellular calcium concentrations, thus contributing to neuron injury. Deprivation of oxygen

and glucose during ischemia also contributes to the increase in cytosolic Ca<sup>2+</sup> via NMDA receptor-mediated pathways [105]. Since drugs blocking Ca<sup>2+</sup> channels have been shown to protect cells, Ca<sup>2+</sup> influx is considered as pivotal pathophysiological mechanism during an ischemic insult [106]. Together with the acute leukocyte influx, these neuronal modifications are probably the most relevant events in the pathophysiology of cerebral ischemia/reperfusion [107, 108].

Thus, cannabinoid-related mechanisms might serve as promising candidates for the reduction of neuronal ischemic injury. In particular, AEA and 2-AG have been shown to especially accumulate in the brain ischemic areas [13, 109]. This enhancement occurs exponentially in a time-dependent manner [110], suggesting a potential protective role for endocannabinoids against the neuronal ischemic injury. However, several discrepancies on the activation of different cannabinoid receptors in experimental models of cerebral ischemia have to be clarified. In particular, the activation of CB<sub>1</sub> receptor has been firstly indicated as a neuroprotective strategy in transient cerebral ischemia models [111]. On the other hand, Pegorini and coworkers also showed that treatment with rimonabant (a selective CB<sub>1</sub> antagonist but also a VRI vanilloid receptor agonist) might increase neuroprotection via the activation of this ligand-gated cation channel [112]. These apparently paradoxical results may find an explanation in the different affinities of cannabinoids for their receptors. In fact, depending on the concentrations, cannabinoids might act as both agonists and antagonists for certain receptors in the same time. Importantly, an increase in CB<sub>2</sub> receptor and TRPV1 and a concomitant decrease in CB<sub>1</sub> cerebral expression were observed in mice underwent permanent middle cerebral artery occlusion and intraperitoneally injected with leptin [113]. The improvements of residual neurological disability were associated with reduced infarct volume in brain, suggesting that these receptors might beneficially influence the neuronal ischemic injury [113].

Taking into account these premises, the cannabinoid receptors have been shown to activate defined intracellular pathways in ischemic neurons [111, 114]. Specifically, CB<sub>1</sub> receptor activation triggers several protective signals involving phosphorylation of mitogen-activated protein kinase (MAPK) kinase 1/2 (MEK1/2), extracellular signal-regulated kinase (ERK1/2), and nuclear factor-kappa B (NF-κB) [114, 115]. These intracellular pathways might increase neuronal survival. The first-in-man study, investigating the cannabinoid therapeutic approach on neuroprotection, showed that the intravenous infusion of THC ameliorates the global and regional cerebral blood flow up to 2 h after the infusion of both low (0.15 mg/min) and high (0.25 mg/min) doses [116]. The encouraging therapeutic results of this study are in partial contrast with previous case reports, suggesting a potential relationship between stroke and chronic cannabis abuse in young human beings [117–120]. Importantly, Mateo and coworkers recently confirmed the potential association between cannabis and ischemic stroke recurrence in a young patient, without identifying the underlying pathophysiological mechanisms [121]. Evidence from autopsy examinations and imaging

reports in both human beings and animal models has suggested that cannabis use might provoke cerebral stroke by favouring the development of atrial fibrillation, orthostatic hypotension, and cerebral artery vasospasm [122–124]. In a prospective study enrolling 48 young adults affected by ischemic stroke, Wolff and co-workers also showed that multifocal intracranial arterial stenosis was associated with cannabis consumption in 21% [125]. Therefore, these preliminary results in human beings suggest using caution in the translational therapeutic approach of cannabinoid from animal models. Further clinical studies (possibly using more selective cannabinoid receptor agonist/antagonist) are needed to clarify the potential therapeutic role of these compounds against the ischemic stroke.

## 5. Conclusion

The endocannabinoid system is considered as a major modulator of the cerebral blood flow, neuroinflammation, and neuronal survival. Despite of some controversies, the activation of CB<sub>2</sub> receptor has been shown to reduce cerebral injury associated with acute post-stroke inflammation and leukocyte infiltration. On the other hand, the direct role of CB<sub>1</sub> in neuronal protection has not been clarified yet. Evidence from animal models and *in vitro* studies suggests a global protective role for cannabinoid receptors agonists in ischemic stroke. However, further studies are needed to clarify the role of the recently discovered cannabinoid receptors (such as GPR55 or VR1 vanilloid receptor) in the physiopathology of the infarcted brain and related inflammation. At this regard, both synthetic cannabinoids and endocannabinoids represent extremely promising therapeutic compounds. Since human studies are still missing, we cannot predict the potential clinical benefits of treatments targeting cannabinoid receptors in ischemic stroke. We believe that the “cannabinoid” approach represents an interesting therapeutic strategy still requiring further validations to improve neurologic and inflammatory outcomes in ischemic stroke.

## Conflict of Interests

The authors declare that they have no conflict of interests.

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