The endocannabinoid system: role in skeletal muscle and regenerative myogenesis

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ABSTRACT

The endocannabinoid system (ES) is a complex network consisting of receptors, mainly cannabinoid receptor (CB) 1 and CB2, endocannabinoids, and enzymes responsible for synthesizing and degrading endocannabinoids. The ES is present in various tissues, including skeletal muscle, which has a high regenerative capacity due to the presence of satellite cells (SCs). These cells are usually inactive, but following injury, they become activated, re-enter the cell cycle, and participate in the repair of the damaged area. This complex process is tightly controlled by muscle regulatory factors, which determine the myogenic lineage. In recent years, the ES has been shown—both *in vitro* and *in vivo*—to regulate SCs proliferation and differentiation through various mechanisms. Notably, CB1 activation in SCs impairs myogenic differentiation, whereas CB2 activation has the opposite effect. Understanding the role of the ES in muscle regeneration could advance research into the therapeutic potential of various components of *Cannabis sativa* for currently incurable muscle diseases. The aim of this concise review is therefore to examine the role of the ES in SCs and the molecular mechanisms through which it regulates muscle regeneration.

KEYWORDS

Endocannabinoid system, cannabinoids, satellite cells, skeletal muscle, skeletal muscle regeneration.

Introduction

The endocannabinoid system (ES) is a complex network consisting of endocannabinoids, the enzymes responsible for their synthesis and degradation, and receptors. The endocannabinoids most studied to date are anandamide (AEA) and 2-arachidinoylglycerol (2-AG) [1].

AEA, the first endocannabinoid described, is synthesized from N-acyl phosphatidylethanolamine (NAPE) by NAPE phospholipase D and is inactivated into arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH) [2,3].

2-AG, the most abundant endocannabinoid, is synthesized from diacylglycerol through the action of diacylglycerol lipase, and hydrolyzed into glycerol and arachidonic acid through that of monoacylglycerol lipase [2,3].

The main receptors in this system, cannabinoid receptors CB1 and CB2, belong to the G-protein-coupled receptor (GPCR) superfamily characterized by seven transmembrane domains, and they are generally coupled to heterotrimeric Gi/o proteins. Consequently, their activation leads to inhibition of adenylate cyclase activity and reduction of cyclic adenosine monophosphate levels [4].

However, in addition to CB1 and CB2, endocannabinoids have also been shown to bind to and activate other receptors. These include those of the transient receptor potential (TRP) superfamily of cation channels, particularly the vanilloid receptor 1 (TRPV1), as well as members of the G protein-coupled receptor superfamily, such as GPR55 [5,6]. TRPV1 is a non-selective cation channel with six transmembrane domains that is activated by low pH, noxious heat, and capsaicin (a compound present in chili peppers), and in skeletal muscle controls the uptake of glucose [7,8]. GPR55 interacts with endocannabinoids, lysophosphatidylinositol, and arachidonoyldopamine [9]. Figure 1 shows the different components of the ES.

Cannabinoid receptors are present in various organs and tissues, and indeed the ES plays a crucial role in the regulation of important physiological functions, such as pain, inflammation, metabolism, and homeostasis [10]. The various cannabinoid receptor families are also activated by phytocannabinoids and synthetic cannabinoids. Phytocannabinoids are natural bioactive compounds found in the resin produced by the female *Cannabis sativa* plants [11]. To date, more than 120 molecules belonging to the phytocannabinoid class have been identified, of which the best known and most extensively studied are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [11,12].

THC is responsible for the psychoactive effects of *Cannabis sativa* [13]; however, it has also been shown to act as an anti-nausea agent, and an appetite stimulant, and to reduce chron-

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ic pain and muscle spasticity [6,14]. CBD has the better safety, efficacy, and tolerability profile, as demonstrated in numerous preclinical and clinical studies. It also has anti-inflammatory and anticonvulsant properties. In fact, it is used to treat epilepsy in children and adults alongside other treatments [6,15]. Synthetic cannabinoids are made in the laboratory and can act as agonists or antagonists of cannabinoid receptors.

Since receptors and other ES components were identified in rodent and human skeletal muscle cells, interest in studying the ES in skeletal muscle has grown [8]. Although endocannabinoids are known to contribute to reducing glucose uptake and to downregulating oxidative pathways in skeletal muscle [16], little is known about the involvement of the ES in myogenic differentiation. Therefore, the aim of this concise review is to investigate its role in satellite cells (SCs) and in muscle regeneration during myogenic differentiation following injury or degeneration.

Functions of skeletal muscle SCs

Skeletal muscle possesses a remarkable natural plasticity that enables it to respond and adapt to various stimuli—for example, growing and repairing itself following injury or tissue damage [17]. Muscle regeneration is a highly complex process, primarily involving SCs, a small population of mononuclear cells located between the basal lamina and the plasma membrane of myofibers [18].

Under normal conditions, SCs in adults are in a quiescent state [19]. However, following a muscle injury, they exit their state of mitotic inactivity, become activated by re-entering the cell cycle, and proliferate to generate myoblasts [20]. The latter differentiate into mature muscle cells, which fuse with those present in the damaged area to form multinucleated myofibers [21].

This is a very complex process, finely regulated by the expression of Paired Box 7 (PAX7) and muscle regulatory factors (MRFs), whose variable and coordinated expression determines the myogenic lineage [22]. PAX7, expressed by all SCs, is crucial for muscle regeneration as it regulates genes involved in activating proliferation and inhibiting differentiation. The MRFs, on the other hand, are a group of four muscle-specific transcription factors—myogenic factor 5 (Myf-5), myogenic differentiation 1 (MyoD-1), myogenic regulatory factor 4 (MRF4) and Myogenin—involved in the various steps of myogenic lineage determination (i.e., SC activation, myoblast proliferation, and myoblast differentiation through to the formation of new muscle fibers) [23,24]. In the final stage of differentiation where new myofibers fuse with existing ones, the expression of mature muscle-specific genes, such as myosin heavy chains (MHC), increases in myogenic cells [25].

However, activated SCs can exit the cell cycle and return to a quiescent state, thus ensuring that a small population of SCs, for the initiation of a new myogenic process, is always maintained [24]. This is possible because in a subpopulation of SCs the expression of PAX7 remains unchanged and that of MyoD-1 decreases [26,27].

Figure 2 shows the various phases of muscle regeneration and highlights the key myogenic regulators that govern this process.

Figure 1 The components of the endocannabinoid system. NAPE: N-acyl phosphatidylethanolamine; NAPE-PLD: NAPE phospholipase D; AEA: anandamide; AA: arachidonic acid; FAAH: fatty acid amide hydrolase; DAG: diacylglycerol; DAGL: diacylglycerol lipase; 2-AG: 2-arachidinoylglycerol; MAGL: monoacylglycerol lipase; CB1: cannabinoid receptor 1; CB2: cannabinoid receptor 2; TRPV1: transient receptor potential vanilloid receptor-1; GPR55: G protein-coupled receptor 55. (Image created with BioRender software).

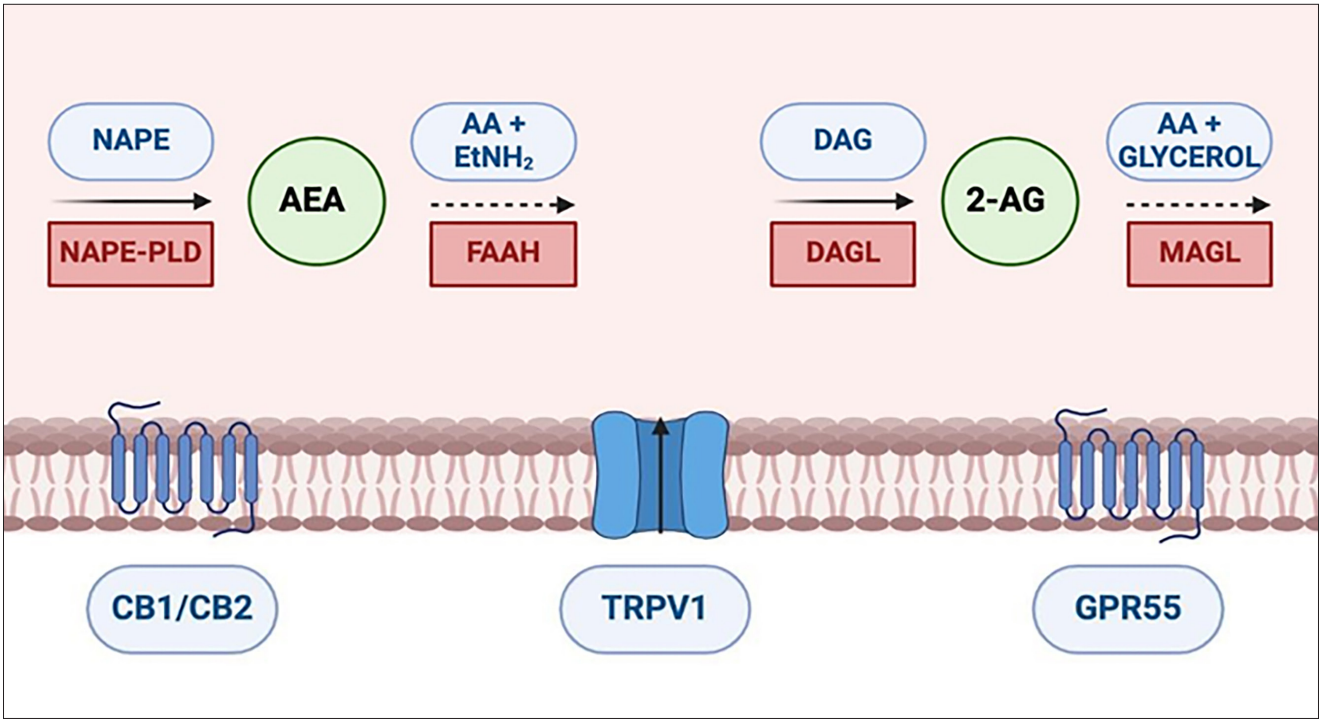
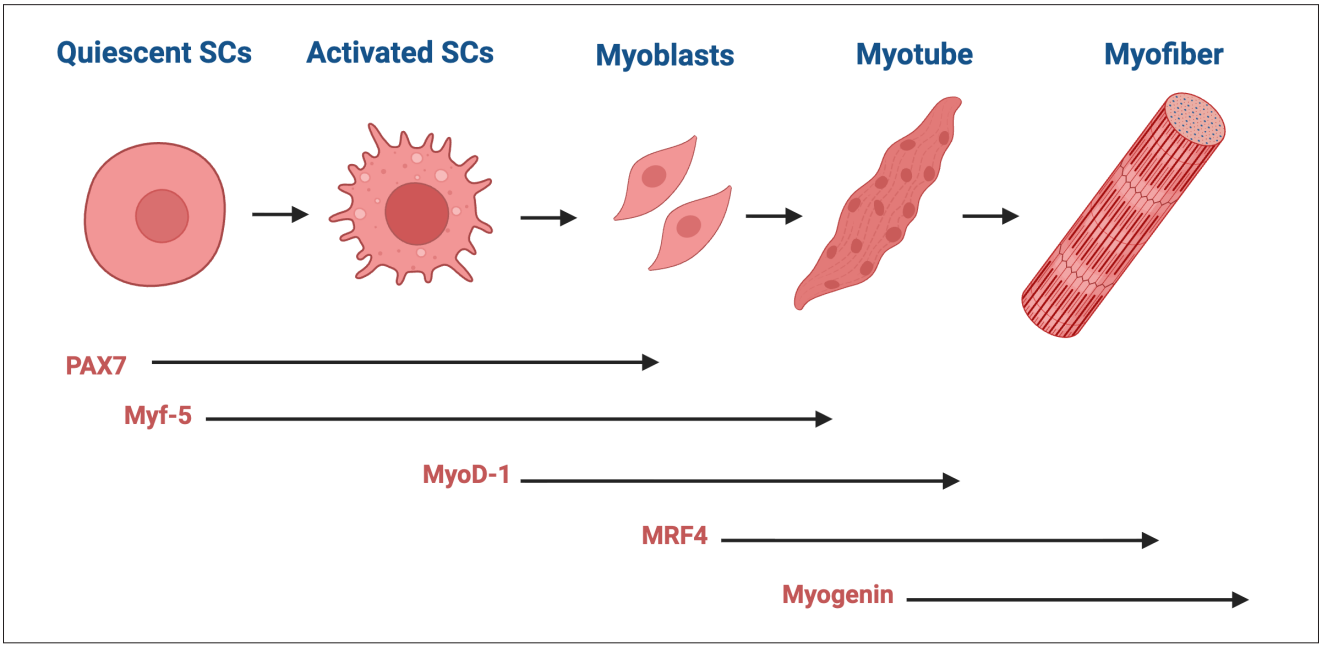


Figure 2 Schematic representation of the myogenic lineage and regulation of key myogenic regulators. SCs: satellite cells; PAX7: Paired Box 7; Myf-5: myogenic factor 5; MyoD-1: myogenic differentiation 1; MRF4: myogenic regulatory factor 4. Image created with BioRender software.



The endocannabinoid system in muscle regeneration

The presence of the ES in human and rodent skeletal muscle was demonstrated as early as the 2000s [28-32]. In particular, Cavuoto *et al*. observed the expression of not only CB1 but also CB2, $TRPV_1$, and FAAH in human and rodent skeletal muscle by RT-PCR, concluding that ES has regulatory effects in this muscle [28].

The ES is actually involved in muscle regeneration through various processes, which have been studied in recent years [33].

In 2009, Eckardt *et al*. highlighted the significance of the ES, particularly CB1, in muscle tissue, having observed increased receptor protein levels during myogenic differentiation in human skeletal muscle cells [30]. Iannotti *et al*. also studied the expression of CB1 and CB2 in murine C2C12 myoblasts and primary human skeletal muscle cells (hSMCs) during myogenic differentiation, showing that CB1 was the most highly expressed receptor and also the one that increased the most during proliferation [34]. To better understand the role of CB1 and CB2 during myogenic differentiation, they treated C2C12 cells and hSMCs with the endocannabinoids AEA and 2-AG, and also with specific agonists and antagonists of these receptors. Treatment with 2-AG (but not with AEA) and with agonists arachidonoyl-2-chloroethylamide (ACEA) and WIN 55,212-2 resulted in a significant reduction in the expression levels of *Myogenin*, *Troponin T1* (Tnnt-1), and *Krp1* (sarcosin), whereas the use of specific CB1 antagonists Rimonabant (now withdrawn from the market due to its serious psychiatric side effects [35]) and AM251 led to a dose-dependent increase in the expression levels of *Myogenin* and *Tnnt-1*. The inhibitory effect on the differentiation process was also confirmed by the decrease in the number and size of MHC red-positive myotubes detected after treatment with 2-AG and ACEA. In addition, the authors investigated whether this decrease could be due to an anti-proliferative effect. However, 2-AG and ACEA resulted in an approximately 30–40% increase in myoblast proliferation. Therefore, the decrease in fibers can be attributed solely to an alteration of the myogenic differentiation process.

The same research group then studied the effects of Rimonabant and ACEA in mdx mice, the main animal model used to study Duchenne muscular dystrophy (DMD), assessing muscle strength and coordination [36]. Rimonabant prevented loss of motor coordination and allowed recovery of strength. In particular, following isolation of skeletal muscle cells from mdx mice, it was demonstrated that Rimonabant increased the number and size of regenerated myofibers, as well as the expression of *MHC* and inflammatory markers, including *tumor necrosis factor*-α (TNF-α), *transforming growth factor*-β (TGF-β), and *inducible nitric oxide synthase*.

Similar results were obtained in C57BL/6 mdx mice and in aged mice, which is relevant from the perspective of efforts to prevent muscle loss and thus maintain physical function and preserve quality of life—in humans as well [37,38]. Rimonabant not only prevented loss of muscle strength but also increased the size of regenerating myofibers [37,38]. Although Rimonabant reduced apoptotic and inflammatory markers, it led to an increase in *PAX7* expression levels, while expression of *Myogenin*, *MyoD-1* and *MHC* remained unchanged [37].

Impairment of myogenic differentiation following CB1 activation could be linked to the fine balance of factors regulating this process [39]. Specifically, CB1 ablation in mice resulted in decreased *Myostatin* but increased *interleukin-* (IL-) *6* expression. This is very interesting because Myostatin inhibits myoblast proliferation and differentiation (regulates muscle mass through the inhibition of protein kinase B phosphorylation and the phosphorylation of small mothers against decapentaplegic 2-3 proteins [40]), whereas IL-6 promotes differentiation (regu-

lates myogenesis through mitogen-activated protein kinase signaling [41]). Thus, CB1 could control myogenic differentiation by regulating the balance between *Myostatin* and *IL-6* expression levels.

CB2 is also involved in the process of muscle regeneration [33]. This has also been demonstrated in myofibroblasts and macrophages during the healing of skeletal muscle contusions [42,43]. Yu *et al*. [42] investigated whether CB2 could play a role in regenerating damaged muscle tissue in rats. After sustaining damage, rats were divided into three groups based on their treatment: vehicle, selective CB2 agonist (JWH-133), and selective CB2 antagonist (AM-630). Treatment with JWH-133 reduced fibrotic areas and the expression of fibrogenic markers compared with the vehicle and the AM-630, which produced the opposite effects. Overall, activation of CB2 with the selective agonist demonstrated that this receptor is involved in not only muscle regeneration but also inhibition of fibrosis following injury.

The positive effects of CB2 activation have been demonstrated in C2C12 myotubes and C57BL/6 mice undergoing ischemia-reperfusion injury (IRI) [44]. Zhang *et al*. observed an increase in *CB2* expression levels during differentiation and demonstrated, through increased formation of multinucleated myotubes and increased levels of MHC and Myogenin proteins, a positive effect on myogenic differentiation following activation of this receptor with the agonist AM1241. These results are consistent with those obtained in the animal model. Indeed, treatment with AM1241 ameliorated IRI-induced damage to skeletal muscle, increasing the number of regenerating fibers and the protein levels of MyoD-1 and Myogenin. The authors attributed the protective effect of CB2 activation to the NF-E2-related factor (Nfr2)-mediated antioxidant response, as this positive effect was reduced by Nfr2 inhibition in both *in vitro* and *in vivo* models. Nrf2 protects cells from oxidative stress by increasing the expression of antioxidant genes, and the latest scientific evidence demonstrates its role in skeletal muscle. CB2 stimulation activates Nrf2, which acts as a transcription factor during myogenic differentiation, causing an increase in *MyoD-1* expression and improving muscle regeneration after IRI [44]. Reduced levels of Nrf2 compromise myogenic differentiation, and Nrf2 knockout mice exhibit slower muscle regeneration [44]. Overall, these data demonstrate that CB2 promotes muscle regeneration by activating Nrf2.

Another mechanism that could explain the beneficial effects of CB2 activation is the reduction of inflammatory processes in wound repair [45]. Treatment with Gp1a, a highly selective CB2 agonist, reduced the infiltration of neutrophils and macrophages in rats, as well as the expression of pro-inflammatory (TNF-α, IL-1β, IL-6 and monocyte chemoattractant protein 1) and pro-fibrotic cytokines (IL-4, IL-13, TGF-β and P-decapentaplegic 3). It also increased the expression of anti-fibrotic cytokines (IL-10). Opposite effects were obtained in rats treated with the CB2 antagonist AM630. Overall, these findings suggest that CB2 plays a role in regulating the inflammatory response triggered by skeletal muscle damage, and reducing this response may be related to the anti-fibrotic properties of CB2.

A further mechanism potentially explaining the role of CB2 in myogenesis was proposed by Jiang *et al*. [46]. Deletion of CB2 in mice resulted in impaired skeletal muscle regeneration following injury (as confirmed by decreased MyoD-1 and Myogenin protein levels). As the function and development of stem cells are influenced by the presence of cytokines and chemokines in their microenvironment, the researchers investigated whether this deletion might also affect the infiltration and phenotype of macrophages. Macrophages are divided into the classically activated M1 subtype and the alternatively activated M2 subtype, which secrete pro-inflammatory and anti-inflammatory cytokines, respectively. Notably, CB2 deletion resulted in increased M1 infiltration and decreased M2 infiltration without affecting the total number of infiltrated macrophages in the damaged area. These results provide insight into the protective role of CB2 in skeletal muscle regeneration by regulating the balance between M1 and M2 macrophages.

To our knowledge, a single study has examined the role of $TRPV_1$ during the myogenic differentiation of C2C12 and human myoblasts following treatment with CBD; with cannabidivarin (CBDV), the CBD analogue; and with Δ^9- tetrahydrocannabivarin (THCV), the THC analog [47]. The authors observed increased expression levels of *Myogenin*, *Tnnt-1*, and *MHC* in both C2C12 cells and primary SCs obtained from healthy donors and patients diagnosed with DMD. As phytocannabinoids have been shown to interact with different members of the TRP family, which is involved in the pathogenesis of DMD, the authors investigated this interaction using specific channel agonists and antagonists and measuring the intracellular calcium concentration. They observed that in C2C12 cells, the positive effect on myogenic differentiation is due to $TRPV_1$ involvement, whereas in human SCs, it is due to TRPA1 involvement. These data are very interesting, as they demonstrate how phytocannabinoids, which do not produce a euphoric effect, can be used to treat DMD.

Overall, these data confirm that the ES is involved in myogenic differentiation and muscle regeneration, particularly given the role of the two main CBs. Specifically, CB2 stimulation promotes muscle regeneration, while CB2 inhibition promotes muscle fibrosis, immune cell infiltration, and inflammation. Conversely, CB1 inhibition stimulates differentiation by increasing expression levels of *MRFs*, whereas activation of CB1 has the opposite effect.

Conclusions and future directions

The identification of the ES in skeletal muscle in the 2000s has prompted a growing interest in its role in metabolic regulation and muscle regeneration. In particular, study of the ES in skeletal muscle has revealed how it is affected by currently incurable muscle diseases. These include sarcopenia, a progressive disease involving loss of muscle mass and strength, and cancer cachexia, where muscle degeneration leads to muscle loss and reduced functional capacity [48,49]. Indeed, significant alterations in the expression of the ES gene have been demonstrated in aged rats and cachectic mice, which are used to study sarcopenia and cancer cachexia, respectively. All this suggests a potential therapeutic application of phytocannabinoids [50,51]. The latest scientific evidence demonstrating the positive ef-

fects of phytocannabinoids on DMD is indeed interesting. CBD and CBDV not only promote the myogenic differentiation of human DMD myoblasts into myotubes *in vitro* but also improve locomotor activity and muscle strength in mdx mice. These findings pave the way for research into their possible clinical use. At present, the most comprehensive knowledge on therapeutic use concerns CBD and THC [52]. However, only a limited number of cannabinoids have been tested as drugs to date, as their use is associated with undesirable psychiatric and addictive effects, which over the years have hindered research into this class of compounds and their subsequent clinical application. CBD and THC have been shown to pose a low and moderate risk of addiction, respectively. For this reason, it is important to study not only the therapeutic potential of cannabinoids, but also their safety profile [53]. Nevertheless, the increasing importance of the ES in skeletal muscle tissue and muscle regeneration will encourage further research aimed at identifying new therapeutic targets and developing drugs for various skeletal muscle diseases.

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