SPOTLIGHT REVIEW ARTICLE

Emerging preclinical evidence supports a potential role for cannabidiol in the management of sickle cell disease

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Abstract

Sickle cell disease (SCD) imposes a substantial global health burden, with acute and chronic pain representing a major component of morbidity. Standard pain management, largely opioid-based, carries significant risks and often provides inadequate long-term relief, highlighting an unmet need for alternative analgesics as well as disease modifiers. Medicinal cannabinoids have analgesic and anti-inflammatory properties; most clinical studies so far have used Δ9-tetrahydrocannabinol (THC)-containing products with conflicting outcomes. In contrast, purified cannabidiol (CBD) has a broader spectrum of action beyond the endocannabinoid system, lacks psychoactive effects and associated long-term risks, allows safe dose optimization and can be prescribed legally in many settings. Here, we review evidence for CBD's potential analgesic and disease-modifying properties for the management of SCD. Pain in SCD arises from local tissue inflammation and neuroinflammation, compounded by abnormal pain modulation and pro-nociceptive central nervous system alterations. CBD may attenuate the pathophysiological processes of SCD by modulating pro-inflammatory immune pathways, reducing oxidative stress and suppression of neurogenic inflammation. CBD also has a direct inhibitory effect on afferent nociceptive pathways. Furthermore, CBD has an important pain-modulating role by suppressing excitatory mechanisms in the dorsal root ganglia and central nervous system. Additionally, CBD may modulate pain-processing brain networks and attenuate opioid-induced reward-seeking behavior. Although human data are very limited, emerging preclinical findings and early reports on patients offer cautious optimism for CBD as a therapeutic option with potential disease-modifying properties in SCD. Clinically meaningful benefits may be expected in specific subgroups of patients, identifiable through well-designed clinical and mechanistic studies focused on pain processing and neuroinflammation.

Introduction

Sickle cell disease (SCD) represents a significant global health burden.[1] For many individuals living with SCD, pain represents the dominant challenge. Acute pain episodes, or vaso-occlusive crises, are the hallmark of SCD, while chronic pain is common and often multifactorial, including clear underlying organic causes (avascular necrosis) as well as peripheral and central nervous system changes secondary to recurrent vaso-occlusive crises.[2] Effective treatment strategies are limited. Hydroxycarbamide is currently the only disease-modifying therapy available in the UK and Mainland Europe. *Curative* approaches, such as stem cell transplant and gene therapy, are only available to the most severely affected in high-income countries, leaving most patients with few therapeutic options. Effective, durable pain management therefore remains a major unmet need, as current high-dose opioid strategies are often inadequate and carry substantial long-term risks.[3]

Cannabis-based therapies are gaining increasing interest in SCD. Medicinal cannabinoids predominantly comprise the psychoactive Δ9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD). Initial reports of symptom relief by users of recreational cannabis[4] have been complemented by clinical trials in several chronic pain conditions, showing mixed but promising evidence.[5] However, many studies to date have encountered methodological challenges, including legislative barriers, variable product composition and heterogenous administration protocols.[5] In SCD, only a handful of studies have examined the efficacy of cannabis, showing moderate symptom relief (Table 1).[6-10] An overview of the components of cannabis and their regulatory status[11] is presented in Figure 1, alongside practical background information

Table 1. Human clinical trials of cannabinoids in sickle cell disease.

Year	Author	Cannabinoid type, administration route and dose	Study design	Findings
2020	Abrams *et al.*[6]	- Non-pharmaceutical grade, 1:1 THC:CBD - Vaporized - 3 times daily, no dosing information	Randomized, double-blind, placebo-controlled crossover N_{SCD} = 27	No significant reduction in pain over 5 days; improvement in mood interference only
2020	Curtis *et al.*[7]	- Non-pharmaceutical grade medical cannabis of variable composition - Variable administration route - No dosing information	Retrospective pre-post case-control N_{SCD} = 29 $N_{control}$ = 25	Obtaining medical cannabis associated with fewer hospitalizations; opioid use unchanged
2020	Curtis *et al.*[8]	- Certified non-pharmaceutical grade medical cannabis of variable composition - Variable administration route - No dosing information	Cross-sectional observational N_{SCD} = 49 (22 users; 27 non-users)	Daily users reported worse pain but had fewer admissions and emergency department visits than matched non-users; opioid use similar
2024	Aron *et al.*[9]	- Certified non-pharmaceutical grade medical cannabis of variable composition - Variable administration route - No dosing information	Retrospective pre-post N_{SCD} = 36	Emergency department visits and admissions decreased pre–post, 44% of patients reported subjective benefit*
2025 (ongoing, interim analysis reported)	Liu *et al.*[10]	- Pharmaceutical-grade THC (dronabinol) - Oral administration - 5-10 mg twice daily	Randomized, double-blind, placebo-controlled parallel group N_{SCD} = 30 (1 THC: 1 placebo)	Measures of pain and quality of life better in dronabinol group, but not statistically significant. Social impact score** significantly better in dronabinol group

*The authors interpreted patients requesting recertification for medicinal cannabis as an indication that they perceived a benefit. Feedback from patients included improvement of pain and/or other symptoms, decreased opioid requirements, and fewer side effects than with opioids. **The PROMIS Social Impact score is a validated measure that reflects how much a person's health limits their ability to participate in usual social roles and activities, such as work, relationships, and community engagement. (*https://www.healthmeasures.net/explore-measurement-systems/promis*). CBD: cannabidiol; SCD: sickle cell disease; THC: Δ9-tetrahydrocannabinol.

on clinical effects, toxicity and dosing strategies (*Online Supplementary Tables S1* and *S2*).

Rationale for the therapeutic use of cannabidiol

Medicinal cannabis exerts anti-inflammatory and anti-oxidant effects through the combined action of THC and CBD. However, clinically relevant THC concentrations in unrefined cannabis may limit clinical applicability (*Online Supplementary Table S2*) and constrain dose optimization due to THC-related adverse effects and potential long-term risks. Notably, CBD exerts broader anti-inflammatory and anti-oxidative effects than those of THC,[12] and in its purified form, permits dose optimization without THC-related risks.[5] In SCD, CBD may have both disease-modifying and anti-nociceptive effects, resulting in a potential to reduce opioid requirements.[13] While a recent case study reported striking pain reduction in a SCD patient with opioid-refractory pain following treatment with purified CBD,[14] the broader clinical evidence for CBD in pain management remains inconclusive (Table 2).[13-28] Across various pain etiologies, six of nine randomized trials and four experimental pain studies have failed to demonstrate superiority over placebo. Notably, null findings were common in trials using single or low doses (10-20 mg), while symptom relief was more commonly observed in repeated-dosing studies. Interpretation is further complicated by CBD's highly complex pharmacokinetics (*Online Supplementary Tables S3* and *S4*). The mechanistic basis of CBD analgesia and whether efficacy differs across pain subtypes remain unestablished.

As clinical trials investigating CBD in SCD emerge, with the first double-blind, placebo-controlled dose-finding study using CBD (ClinicalTrials.gov ID NCT06930703) recently commencing recruitment, this narrative spotlight review highlights the potential therapeutic mechanisms of CBD in SCD. We focus on CBD's interactions with anti-inflammatory pathways and its effects on nociception and pain processing in the central nervous system (CNS).

Interplay between inflammation, nociception and modulation

Pain in SCD arises from complex, multi-level interactions. Vaso-occlusion, hemolysis and tissue inflammation[29] ac-

CANNABIS - COMPOSITION

The cannabis plant (cannabis sativa) comprises a complex phytochemical profile, containing hundreds of compounds. The principal classes of relevance are:

1. (Phyto)cannabinoids
These are bioactive compounds unique to cannabis. The two most clinically and pharmacologically relevant are:

- **Δ9-tetrahydrocannabinol (THC)**
  THC is predominantly derived from marijuana-type plants. It is psychoactive and responsible for the characteristic euphoric "high". THC can be administered via multiple routes, including inhalation (smoked or vaporized plant material), oral ingestion (oils, edibles, infusions), and topical formulations (creams, resins). Most THC-containing products also include variable concentrations of cannabidiol. Pharmaceutical-grade THC is available as synthetic or plant-derived formulations, typically in capsule or oromucosal spray form.

- **Cannabidiol (CBD)**
  CBD is present in both hemp and marijuana plants. It is non-intoxicating and does not produce psychoative effects, and is therefore not typically sought for recreational use. CBD products may contain trace or variable amounts of THC depending on preparation. Routes of administration include inhalation, oral, transdermal, and rectal delivery. Commercial formulations include oils, capsules, vaporized products, topical preparations, and food supplements. Pharmaceutical-grade CBD is available as purified, plant-derived oral oil.

2. Terpenes
Terpenes are volatile aromatic compounds responsible for the characteristic scent and flavor of cannabis (e.g., limonene, myrcene, pinene). They are not intoxicating.

3. Flavonoids
Flavonoids are plant-derived polyphenolic compounds with antioxidant properties. They are non-psychoactive.

CANNABIS - REGULATORY VARIABILITY

Cannabinoids have historically been classified as controlled substances (e.g., Schedule 1) in many jurisdictions, including the UK, EU, and USA, reflecting concerns regarding misuse and lack of recognized medical utility. However, regulatory frameworks have evolved substantially:

- Recreational use is now legally permitted in several countries and multiple U.S. states.
- Medicinal use is authorized in many regions, though subject to jurisdiction-specific controls, often including requirements for specialist prescription, licensing, or dispensing through regulated providers.
- CBD products are generally less tightly regulated, provided THC content remains below defined thresholds (commonly 0.2–0.3%), although classification may vary between "novel foods", supplements, or medicines depending on claims and formulation.
- Non-cannabinoid constituents (e.g., terpenes and flavonoids) are typically not subject to specific legal restrictions.

Overall, there remains substantial international heterogeneity in regulatory approaches, with implications for product quality, prescribing practices, and patient access.

Figure 1. Overview of cannabis components and their regulatory framework.

tivate afferent sensory nerve fibers, including nociceptive and mechanosensory pathways (Figure 2). Locally, nociceptive signaling can be amplified by the release of neuropeptides, such as substance P, and by neurogenic inflammation, driven by interactions between sensory nerves and immune cells.[30] In SCD, recurrent ischemia–reperfusion injury, oxidative stress and chronic immune activation predispose to exaggerated neuroinflammatory responses.[29] Nociceptive signals are subsequently modulated in the dorsal root ganglia, spinal cord and brain, where sensitization and inhibitory processes shape how pain is ultimately perceived, sometimes independently of the initial stimulus.[30] The following sections describe how CBD can influence inflammation and pain processing across multiple levels.

Background: the endocannabinoid system and cannabinoids

THC and CBD modulate the endocannabinoid system (ECS), activating its downstream signaling pathways. The ECS consists of cannabinoid type-1 and type-2 receptors (CB1R and CB2R), endocannabinoids (e.g., anandamide, 2-arachidonoylglycerol) and their synthesizing and degrading enzymes. The ECS regulates homeostasis by modulating neurotransmission, inflammation, pain, metabolism and stress responses (for a detailed review see Pertwee *et al.*[31]). Both CB1R and CB2R are G-protein coupled receptors (GPCR) but differ in tissue distribution and downstream effects. CB1R are abundantly present in the CNS and, to a lesser extent, in the peripheral nervous system. CB1R activation has presynaptic effects on

Table 2. Clinical studies evaluating oral cannabidiol for pain management in humans.

Year	Author	Indication and administration route/dose	Study design	Findings
Clinical trials				
2020	Capano *et al.*[13]	- Chronic pain patients on a stable opiate dose - 15-60 mg of hemp CBD (containing approx. 3% THC) for 8 weeks	Prospective, single-arm cohort study N=97	53% able to reduce or eliminate opioids by week 8 94% reported improved quality of life outcomes
2021	Bebee *et al.*[15]	- Acute back pain in emergency department (CANBACK trial) - Single-dose oral 400 mg or placebo	Randomized, double blinded, placebo-controlled clinical trial N=100 (50 CBD, 50 placebo)	CBD not superior to placebo
2022	Vela *et al.*[16]	- Chronic osteoarthritis or psoriatic arthritis (NordCAN) - Daily CBD 10 mg, increasing to twice daily after 14 days, or placebo	Randomized, placebo-controlled double-blinded study N=129 (68 CBD, 61 placebo)	CBD not superior to placebo
2022	Alaia *et al.*[17]	- Post-arthroscopic rotator cuff repair - Transbuccal CBD 25-50 mg 3 times daily for 14 days, or placebo	Randomized, double-blind, placebo-controlled trial N=99 (52 CBD, 47 placebo)	Superior pain control for first 2 post-operative days with CBD in comparison with placebo
2023	Narang *et al.*[18]	- Post-ureteroscopic stent placement analgesia - Daily CBD 20 mg for 3 days, or placebo	Randomized, double-blind, placebo-controlled trial N=90 (45 CBD, 45 placebo)	CBD not superior to placebo
2023	Rossignol *et al.*[19]	- Chronic mastocytosis-related pain - Daily CBD 50 mg, titrated to 900 mg daily over three divided doses for 3 months	Open label, non-interventional, prospective pilot study N=44	Pain scores (0-10) decreased from 7.3 before to 4.3 after 1 month of treatment and 3.8 after 3 months of treatment
2024	Chrepa *et al.*[20]	- Acute dental pain - Either single-dose CBD 10 mg/kg, 20 mg/kg or placebo	Randomized, placebo-controlled double-blinded study N=61 (40 CBD, 21 placebo)	CBD improved pain and bite force in comparison with placebo
2025	Fleege *et al.*[21]	- Aromatase inhibitor-associated joint pain in breast cancer - Twice daily CBD titrated to 100 mg for 15 weeks	Open label pilot study N=39 (28 completed protocol)	61% reported at least a 2-point improvement of the Brief Pain Inventory score (range, 0-10) Significant reduction in inflammatory markers at week 15; not predictive for CBD response
2026	Rasmussen *et al.*[22]	- Pain relief in fibromyalgia - CBD 50 mg daily, or placebo for 24 weeks	Randomized, double-blind, placebo-controlled trial N=200 (100 CBD, 100 placebo)	CBD not superior to placebo
Human pain model studies				
2021	Arout *et al.*[23]	- Experimental acute pain - Single-dose CBD 200-800 mg, or placebo	Double-blind, placebo-controlled, within-subject study N=17	CBD not superior to placebo. CBD 800 mg decreased pain threshold
2022	Schneider *et al.*[24]	- Experimental acute pain (CANAB I trial) - Single-dose oral 800 mg or placebo	Randomized, placebo-controlled, double-blinded, crossover study in healthy volunteers N=20	CBD not superior to placebo
2024	Dieterle *et al.*[25]	- Experimental acute opiate-induced hyperalgesia (CANAB II trial) - Single oral dose of 1,600 mg or placebo	Randomized, placebo-controlled, double-blinded, crossover study in healthy volunteers N=24	CBD not superior to placebo

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Year	Author	Indication and administration route/dose	Study design	Findings
Human pain model studies				
2025	Bergeria *et al.*[26]	- Experimental acute pain - Single dose of hydromorphone 4 mg, with either CBD 50 mg, CBD 100 mg, CBD 200 mg, or placebo	Double-blind, placebo-controlled, within-subject study N=31	CBD added to hydromorphone enhanced analgesia. CBD 50 mg had the best balance between effect and side effects
Case reports				
2025	Russo *et al.*[27]	- Severe pain in mastocytosis - Titration to CBD 100 mg twice daily	Case report N=1	80% overall reduction of pain symptoms
2024	Tadei[28]	- Spondyloarthritis-related neuropathic pain - Titration to CBD 100 mg twice daily	Case report N=1	Improvement after 20 days (dose level 50 mg twice daily) Full resolution of pain after 90 days
2023	Mayrand *et al.*[14]	- Refractory pain in sickle cell disease - Titration to CBD 22 mg/kg (in 3 doses)	Case report N=1	Complete regression of pain after 14 days

CBD: cannabidiol; THC: Δ9-tetrahydrocannabinol.

both excitatory (glutamatergic) and inhibitory (GABAergic) neurons.[31] In contrast, CB2R are predominantly found on immune cells, with CNS expression limited to microglia and dopaminergic neurons in the basal ganglia. CB2R activation mainly has immunomodulatory effects and indirectly reduces (neuro-) inflammation and excitability by suppressing pro-inflammatory cytokines. The ECS also encompasses other, less well-described GPCR that fall outside the scope of this review.

While CB1R activation produces dose-dependent analgesia in neuropathic pain, it also shows psychoactive effects.[31] Furthermore, chronic or heavy stimulation of CB1R by THC increases the risk of dependency and persistent cognitive deficits.[31] On the other hand, CB2R activation promotes anti-inflammatory, neuroprotective and analgesic effects. CB2R agonists suppress pro-inflammatory cytokine release, limit immune cell migration, attenuate neuropathic pain, reduce microglial activation and may slow progression in neurodegenerative conditions.[12] Unlike THC, CBD has additional affinity for a multitude of receptors beyond the canonical ECS, regulating inflammation, metabolic processes and pain perception.[12] As such, purified CBD is a more promising therapeutic agent than whole cannabis or THC alone.

Potential targets for cannabidiol within the pathophysiology of sickle cell disease

Vaso-occlusion and hemolysis cause oxidative stress and chronic inflammation, disrupting multiple cellular signaling pathways that promote tissue damage, pain and further vaso-occlusion. Downstream effects are further amplified by activation of pro-inflammatory cascades, hypoxia–reperfusion injury and the deleterious actions of free heme released during hemolysis.[29] The following sections outline preclinical evidence demonstrating how CBD modulates the pathophysiological processes involved in SCD (Figure 2).

The effect of cannabidiol on neurogenic inflammation and mast cells

Vaso-occlusion causes local injury, which triggers peripheral nociceptors.[32] C-fiber nociceptors transmit noxious stimuli to the CNS and mediate efferent responses that trigger vasodilation and plasma extravasation (i.e., neurogenic inflammation). When activated, their action potentials travel both toward the CNS and antidromically to peripheral terminals, releasing neuropeptides, substance P and calcitonin gene-related peptide, potentiating further local nociceptor activity.[30]

Mast cells play an important role in SCD pathophysiology.[29] Mast cell activation, triggered by the presence of vaso-occlusion-related cytokines and hemolysis-related cell-free heme,[33] results in tryptase release. Tryptase in turn can cause further nociceptor excitation via protease-activated receptor 2 (PAR2), a GPCR present on sensory neurons. This results in further increase of substance P release,[34] contributing to additional C-fiber stimulation. Mast cells express both CB1R and CB2R. In an SCD rodent model (HbSS-BERK mice), CBD-mediated inhibition of mast cell activation via these receptors was associated with reduced serum tryptase and substance P levels, alongside attenuation of allodynia.[34,35]

Apart from direct CBR1/CBR2-mediated inhibition of mast cell activation, CBD can also modulate pain perception by interacting with nociceptive signaling and by mitigating neurogenic inflammation in the mast cell environment. Tryptase-activated PAR2 increases nociception via transient

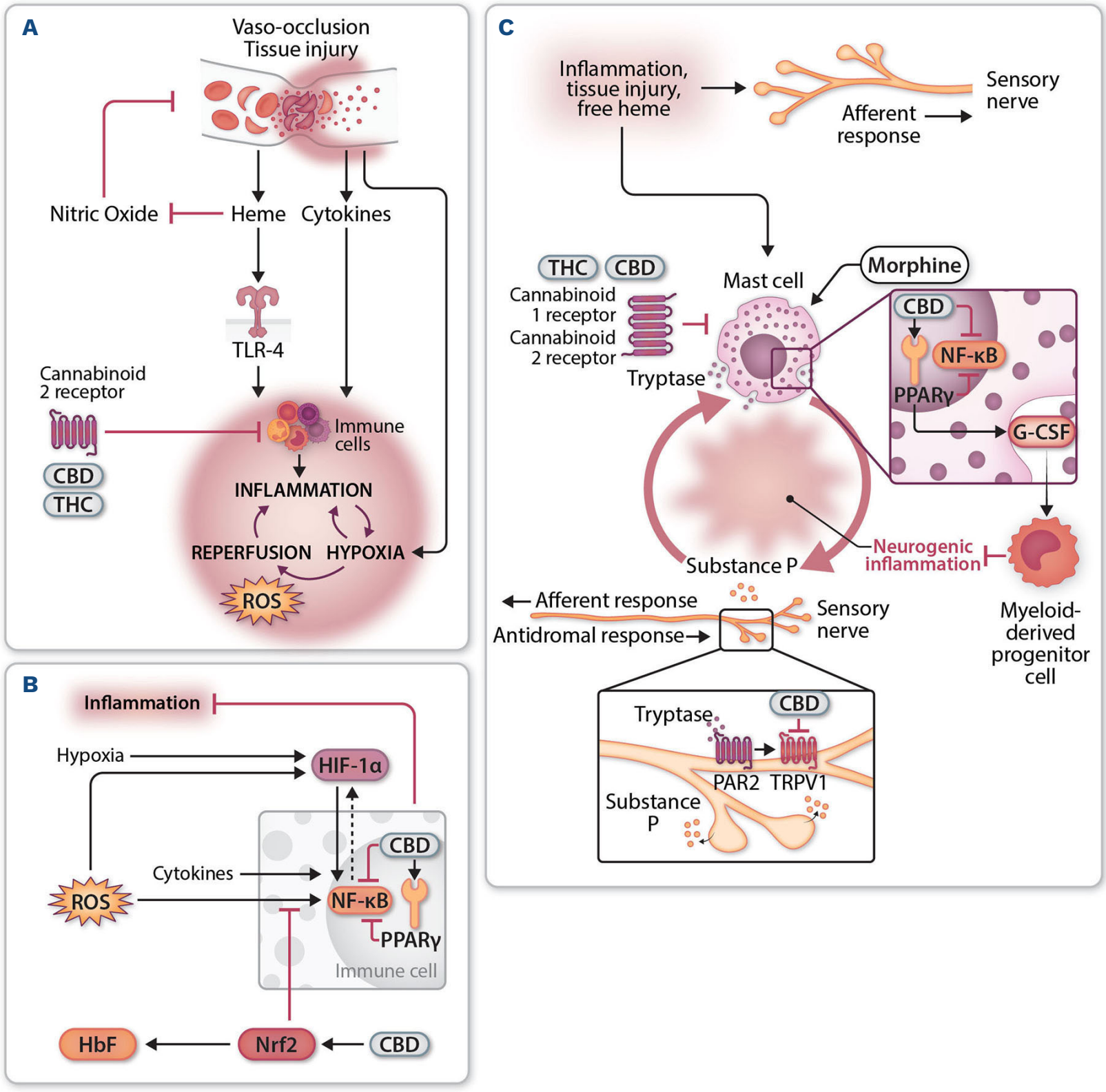


Figure 2. Simplified illustration depicting the interactions of cannabinoids with pathophysiological processes and nociceptive mechanisms in sickle cell disease. (A) Vaso-occlusion and hemolysis result in tissue injury and hemolysis. The subsequent release of cytokines, development of local hypoxia and release of free heme amplify local inflammatory responses, which are further reinforced by reactive oxygen species (ROS) generated by hypoxia–reperfusion injury. Peripheral immune cells express CB2R, and CB2R agonist signaling exerts predominantly anti-inflammatory effects. (B) CBD also attenuates inflammation independently of the endocannabinoid system. At the nuclear level, a key driver of pro-inflammatory signaling is NF-κB. During vaso-occlusion, pro-inflammatory cytokines, ROS, and hypoxia – mediated in part via HIF-1α – promote upregulation of NF-κB activity. CBD can inhibit the NF-κB pathway directly, but also indirectly through activation of PPARγ, a major suppressor of pro-inflammatory signaling, including NF-κB. In parallel, CBD can upregulate Nrf2, a master regulator of cellular antioxidant responses. Activation of Nrf2 may mitigate oxidative stress–driven pathology in sickle cell disease and could, at least theoretically, contribute to upregulation of fetal hemoglobin expression. (C) Inflammation, tissue injury, and the release of free heme initiate an afferent nociceptive response through activation of local sensory nerve endings. These stimuli also activate mast cells, leading to the release of mediators such as tryptase, which in turn further activates nociceptive sensory fibers. Activation of nociceptive nerve endings results in the release of substance P, a key mediator of neurogenic inflammation and a potent activator of mast cells, thereby establishing a feed-forward inflammatory loop. In addition, morphine – commonly used in the management of sickle cell–related pain – can directly activate mast cells, independently amplifying this process. Antidromal signaling within primary sensory neurons promotes additional peripheral release of substance P, further contributing to neurogenic inflammation. Mast cell activation can be attenuated through the endocannabinoid system, as mast cells express both CB1R and CB2R. CBD exerts additional mast cell–modulating effects independent of the endocannabinoid system, notably via inhibition of NF-κB signaling and activation of PPARγ. In mast cells, PPARγ signaling – enhanced by CBD – also promotes recruitment of myeloid-derived progen-

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itor cells with inhibitory effects on neurogenic inflammation. Separately, CBD dampens nociceptive signaling by reducing neuronal sensitivity through blockade of TRPV1. CB1R: cannabinoid receptor 1; CB2R: cannabinoid receptor 2; CBD: cannabidiol; G-CSF: granulocyte colony-stimulating factor; HbF: fetal hemoglobin; HIF-1α: hypoxia-inducible factor-1 alpha; NF-κB: nuclear factor kappa-B; Nrf2: nuclear factor erythroid 2–related factor 2; PAR2: protease-activated receptor 2; PPARγ: peroxisome proliferator-activated receptor gamma; ROS: reactive oxygen species; SCD: sickle cell disease; THC: Δ9-tetrahydrocannabinol; TLR4: Toll-like receptor 4; TRPV1: transient receptor potential vanilloid 1.

receptor potential vanilloid 1 (TRPV1) signaling.[34] TRPV1 has a regulatory role in nociception and is expressed in sensory neurons in several tissues, including dorsal root ganglia. Increased TRPV1 signaling contributes to enhanced nociceptor excitability and peripheral sensitization and has been linked to thermal hypersensitivity and neurogenic inflammation.[30] Through sustained afferent input, it may also contribute to central sensitization and the development of mechanical allodynia.[30] CBD is a TRPV1 agonist causing rapid desensitization, thus inhibiting the TRPV1-induced nociception.[36]

The immune-modulatory effects of CBD on mast cells can be attributed to peroxisome proliferator-activated receptor (PPAR) signaling. PPAR are nuclear receptors governing metabolism, homeostasis, inflammation and immunity. One type, PPARγ, is highly expressed on adipocytes and immune cells, including macrophages and mast cells. Its activation results in suppression of pro-inflammatory signaling, including the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway.[37] Intracellular CBD acts as a ligand for PPARγ and has a unique additional downstream consequence in mast cells, inducing the release of granulocyte-colony stimulating factor, which mobilizes myeloid-derived suppressor cells.[38] These cells are immunosuppressive cells that can dampen chronic inflammation and allergic responses. CBD's PPARγ agonism "reprograms" mast cells towards a more quiescent, anti-inflammatory phenotype. Altogether, within the mast cell environment, CBD attenuates neurogenic activation by inhibiting mast cell activation, suppressing nociceptive signaling and exerting immunomodulatory effects.

Mitigating effects of cannabidiol on inflammation and hypoxia-reperfusion injury

Recurrent vaso-occlusive crises generate cycles of mechanical stress, inflammation and hypoxia-reperfusion injury, activating NF-κB pathways.[39] NF-κB is referred to as the "central inflammatory switch". Upon activation, NF-κB translocates to the nucleus, driving transcription of cytokines, adhesion molecules and tissue factor, reinforcing vascular inflammation and endothelial injury. Tissue hypoxia results in hypoxia-inducible factor 1-alpha (HIF-1α) expression.[39]

Crosstalk between HIF-1α and NF-κB creates a pathogenic feed-forward loop. NF-κB upregulates HIF-1α transcription even under normoxic conditions, sustaining a pro-inflammatory environment.[40] This interaction contributes to the persistent endothelial dysfunction, upregulation of adhesion molecules, cytokine release, oxidative stress and vascular occlusion characteristic of SCD.[29] NF-κB activity can be further amplified through MAPK/ERK signaling, which is activated via a number of pathways by oxidative stress, mechanical stress and growth factors.[12] This includes stimulation of the serotonin 5-HT1A autoreceptor (5-HT1AR), a target on which CBD has an antagonizing effect.[12]

CBD is an effective inhibitor of NF-κB activation, although the exact interaction between the NF-κB pathway and CBD is not entirely clear.[12] CBD inhibits release of NF-κB via targeting FKBP5, a key facilitator in the activation process of NF-κB,[41] as well as indirectly via PPARγ activation. Specifically in microglia, inhibition of the NF-kB pathway alleviates neuroinflammation and reduces neuropathic pain and hyperalgesia in rodents.[41] In summary, by inhibiting the NF-κB pathway, CBD has the potential to mitigate the aberrant hyperinflammatory state characteristic of SCD.

Attenuation of downstream effects of hemolysis and oxidative stress by cannabidiol

Chronic hemolysis and recurrent hypoxia-reperfusion generate excessive reactive oxygen species, augmenting endothelial damage, inflammation and further hemolysis. Acute and chronic hemolysis in SCD result in the release of free heme into plasma, causing nitric oxide depletion[29] and stimulation of the innate immune system via toll-like receptor 4 (TLR4), in turn triggering NF-κB signaling and metabolic reprogramming of macrophages towards a pro-inflammatory M1 phenotype.[42] In a murine model, endothelial TLR4 upregulation also promoted vaso-occlusion.[43] In addition, preclinical evidence indicates that cell-free hemoglobin S (HbS), rather than heme or cell-free hemoglobin A (HbA), exerts a more potent pro-inflammatory effect via TLR4 activation, underscoring the heightened inflammatory burden in SCD compared with other hemolytic conditions.[44]

CBD can modulate hemolysis-induced immune responses through inhibition of both NF-κB signaling and heme-induced mast cell activation. In the hypoxic and oxidative stress environment of SCD, the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) controls key counteracting mechanisms that regulate cellular responses and gene expression related to oxidative stress.[45] *In vitro* experiments also identified that Nrf2 plays a role in gamma-globin gene transcription, suggesting that Nrf2 activators induce fetal hemoglobin (HbF) in SCD[45]. CBD promotes Nrf2 activation through multiple indirect pathways. It modulates kinase signaling cascades, including PI3K/Akt and MAPK.[12] In parallel, CBD engages in receptor-mediated crosstalk via PPARγ. Additionally, CBD can induce oxidative stress

signals that release Nrf2 from its inhibitory cytoplasmic "anchor", Keap1.[46] Through this mechanism, CBD attenuates hemolysis-associated oxidative stress, lipid peroxidation and NF-κB–driven inflammation, restoring endothelial redox balance and potentially reducing vaso-occlusive risk. None of the Nrf2-activating studies using CBD has investigated HbF expression.

In brief, the downstream pro-inflammatory consequences of hemolysis and oxidative stress in SCD may be attenuated through CBD's interactions with mast cells and inflammatory signaling pathways. In addition, via activation of the Nrf2 pathway, CBD reduces cellular responses to oxidative stress and could, in theory, have a disease-modifying effect in SCD by promoting HbF production.

The role of the central nervous system in sickle cell disease pain and potential effects of cannabidiol

Neuroimaging evidence increasingly implicates the CNS in the development and maintenance of chronic pain. The neural signature of chronic pain is complex, involving structural and functional alterations in distributed brain and spinal cord regions that mediate sensory, cognitive and affective processing (Figure 3).[47] Emerging evidence demonstrates analogous changes in SCD chronic pain, characterized by an apparent pro-nociceptive bias.[48]

Compared to healthy individuals, SCD patients experiencing persistent pain have reduced volumes of gray and white matter, alongside differential activity in regions of the default mode, salience and sensorimotor networks, including brainstem and cerebellar structures.[48-51] Changes in temporal characteristics of neural function observed in SCD, including slower neural oscillations,[51,52] may also indicate disruption in thalamocortical rhythms frequently implicated in other chronic pain conditions.[53] Chronic pain in SCD is also characterized by altered dynamics of neural activity, manifesting as faster synchronization across regions[54] and heightened sensitivity to transitions between different brain states.[52] Critically, many of these neurofunctional alterations correlate with chronic pain severity and frequency of hospitalization,[51,52] and may predict the onset of vaso-occlusive crises.[52]

These findings suggest that maladaptive neuroplastic changes may contribute to pain chronification in SCD, consistent with preclinical theories of central sensitization wherein the CNS becomes hyperresponsive to somatosensory stimuli.[55] Preclinical models demonstrate heightened spinal nociceptive reactivity,[56] while human SCD studies show elevated glutamate levels in pain-related regions,[57] further implicating alterations in excitatory neurotransmission. Notably, neural differences between cases and controls are more pronounced at rest than during evoked pain, suggesting that persistent pain in SCD arises through complex interactions between alterations in CNS activity, vascular dysfunction and ongoing nociceptive input, rather than nociception alone.[50] These changes parallel those observed in other chronic pain conditions but are likely amplified by SCD-specific factors, including vascular and hypoxic burden of the disease and opioid use.[2,55]

These neurofunctional alterations present plausible targets for CBD. In healthy individuals, CBD modulates the functional connections between the striatum and networks related to pain processing, including associative, salience and sensorimotor networks.[58] These connectivity effects parallel the aberrant brain function in SCD chronic pain[48-51] suggesting potential mechanistic overlap. Neuroimaging evidence from healthy volunteers often localizes CBD's effects to limbic-affective regions, showing modulation of both neural function and cerebrovascular flow.[58] CBD's action on cerebral perfusion may be particularly relevant in SCD, given the underlying vascular pathology and recurrent hypoxic-ischemic infarcts contributing to chronic pain.[2] CBD-related changes in cerebral blood flow may influence pain processing in SCD through improved tissue oxygenation and neurovascular coupling. Beyond its vascular action, CBD's limbic modulation may improve top-down regulation of pain salience and attenuate the affective dimensions of the pain experience. This proposed mechanism aligns with CBD's established anxiolytic effects[59] and parallels the neural effects of THC observed during pain states.[60] Preclinical data further suggest that CBD's limbic modulation may be mediated by CBD desensitizing signaling via 5-HT1AR.[12] The net effect is an increase in serotonin-dependent neurotransmission, which is responsible for both anti-nociceptive and anti-inflammatory effects. CBD may also modulate pain processing at the brainstem and spinal cord level through its interactions with glycine receptors.[61] These receptors mediate inhibitory neurotransmission at the dorsal horn of the spinal cord. Suppression of this signaling increases the excitability of dorsal horn neurons, resulting in increased nociception. In rodent models of inflammatory and neuropathic pain, CBD increased inhibitory glycinergic transmission, thus contributing to analgesic effects.[61]

The molecular mechanisms of CBD's CNS effects, however, remain incompletely characterized, with multiple receptor systems implicated. As outlined above, preclinical evidence indicates that CBD analgesia is related to signaling via serotonergic, vanilloid, glycinergic, PPAR-mediated, cannabinoid and opioidergic pathways, but human studies are lacking.[12,37,61] Furthermore, CBD's capacity to modulate glutamatergic and GABAergic neurotransmission in healthy individuals[58] may attenuate the central hyperexcitability and elevated insula glutamate levels observed in SCD.[52,57] By acting on both affective and sensory pathways, CBD may counteract the maladaptive neuroplasticity observed in SCD chronic pain.

Collectively, these effects of CBD likely influence pain-re-

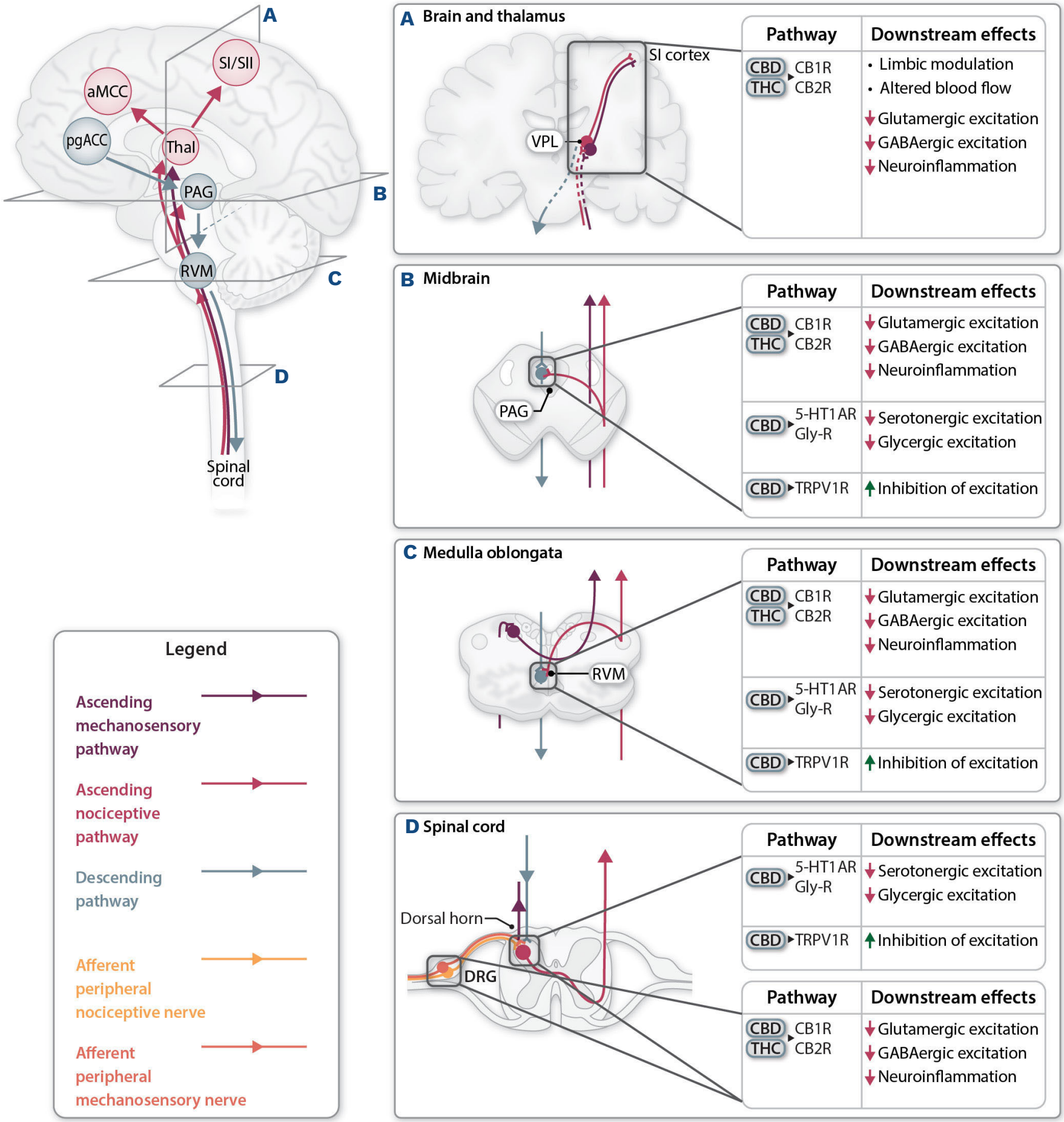


Figure 3. Simplified illustration of the central nervous system depicting how cannabinoids interact with neural pathways involved in pain modulation and the subjective experience of pain. Left. Sagittal cross section of the central nervous system (CNS). Nociceptive and mechanosensory signals ascend from the spinal cord to the thalamus, which relays input to cortical regions involved in the sensory-discriminative (SI/SII) and affective-motivational (anterior mid-cingulate cortex, perigenual anterior cingulate cortex) dimensions of pain. Descending pain modulatory pathways originate in cortical and subcortical regions and project via the periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) to the spinal cord, where they exert inhibitory or facilitatory control over nociceptive transmission. CB1R are widely distributed across the cerebral cortex, hippocampus, thalamus, and basal ganglia, while CB2R are predominantly expressed on microglia throughout the CNS. Cannabinoid signaling at these levels modulates pain perception, influences higher-order pain processing, and contributes to attenuation of chronic neuroinflammation within the CNS. Cross-sections A-D refer to frontal and transverse planes in the right panel, in which these anatomical areas are

Continued on following page.

highlighted in more detail. Right. (A) The thalamocortical pathway relays nociceptive and mechanosensory signals from the ventroposterolateral nucleus of the thalamus to the primary somatosensory cortex (SI cortex). Medial and inferior to the thalamus, the descending pain modulatory pathway projects through the midbrain PAG and medullary RVM, decussating at the spinal cord level to terminate at the contralateral dorsal horn. (B) The PAG in the midbrain is a key hub for descending pain-modulatory pathways. Cannabinoid receptors are densely expressed in this region. In addition, cannabidiol (CBD) modulates neuronal activity via serotonergic and glycinergic signaling and reduces neuronal excitability through inhibition of TRPV1. (C) The RVM in the medulla oblongata is another critical component of descending pain control. Cannabinoid receptors are abundantly present, and CBD further influences pain modulation via serotonergic and glycinergic pathways and by inhibiting TRPV1-mediated neuronal excitation. While ascending afferent mechanosensory fibers decussate at this level, their modulation occurs primarily at the spinal entry point. (D) The dorsal horn of the spinal cord is central to gating incoming mechanosensory and nociceptive input, consistent with the gate control theory of pain. Pain transmission is regulated by descending modulatory pathways and by excitatory and inhibitory interneurons. As at supraspinal levels, CBD modulates interneuronal activity via serotonergic and glycinergic signaling and reduces excitability through TRPV1 inhibition. CB1R/CB2R signaling additionally attenuates pain transmission within the dorsal horn and directly at the level of primary sensory neurons in the dorsal root ganglion. 5-HT1AR: serotonin 5-HT1A autoreceptor; aMCC: anterior midcingulate cortex; CB1R: cannabinoid receptor 1; CB2R: cannabinoid receptor 2; CBD: cannabidiol; CNS: central nervous system; DRG: dorsal root ganglion; GABA: gamma-aminobutyric acid; Gly-R: glycine receptor; PAG: periaqueductal gray matter; pgACC: pregenual anterior cingulate cortex; RVM: rostral ventromedial medulla; SI: primary somatosensory cortex; SII: secondary somatosensory cortex; Thal: thalamus; THC: Δ9-tetrahydrocannabinol; TRPV1R: transient receptor potential vanilloid 1 receptor; VPL: ventroposterolateral nucleus of the thalamus.

lated CNS processing in SCD through a combination of neurovascular, molecular and network-level modulation. These mechanisms converge on both sensory and affective components of pain, suggesting that CBD may exert analgesic effects by reducing the perceived intensity and emotional burden of pain, in addition to peripheral anti-nociceptive and disease-modifying activity.

Attenuation of opioid-related problems by cannabidiol

Morphine is the reference analgesic for acute SCD pain, but the disease's relapsing-remitting nature renders patients vulnerable to opioid dependency, tolerance and opioid-induced hyperalgesia.[3] Opioid-induced hyperalgesia is a complex phenomenon involving desensitization of morphine receptors, aggravated by escalating dose requirements as tolerance develops.[62] Furthermore, morphine may paradoxically worsen pain by directly promoting mast cell activation and degranulation.[63]

CBD may counteract some of the mechanisms related to both opioid dependency and opioid-induced hyperalgesia. Preclinical evidence demonstrated that CBD can reduce opioid-induced reward-seeking behavior via CB1R agonism[31] and 5-HT1AR signaling.[64] Synergistic effects of whole cannabis and opioids have also been observed in small groups of patients with heterogenous chronic pain receiving morphine or oxycodone as part of their routine care, reporting substantial reduction in pain without altering opioid plasma levels.[65]

Importantly, early evidence suggests that CBD may help patients experiencing persistent pain to reduce opioids[13] and significantly reduce the associated withdrawal symptoms.[66] This opioid-sparing potential may represent an important aspect of CBD's therapeutic action in SCD, addressing both the need for effective pain relief and management of opioid-related harm resultant from common treatment options.

Limitations

The CBD evidence base in SCD remains limited, with most insights derived from either preclinical work or human studies relying on acute, single-dose designs that do not reflect chronic clinical use. Investigating dosing regimens that mirror real-world usage is therefore essential. Furthermore, individual differences in analgesic response are likely, potentially influenced by disease phenotype, pain characteristics, psychological factors, placebo/nocebo effects and pharmacokinetic variability, as reflected by the variable outcomes observed to date (Table 2).

Functional neuroimaging may further elucidate SCD pain mechanisms and CBD's therapeutic potential. However, SCD cohorts are heterogeneous, often on analgesics and typically scanned pain-free rather than during clinical meaningful pain states, confounding interpretation. CBD neuroimaging research has been restricted to small, healthy samples, with methodological heterogeneity, dataset reuse and a lack of chronic pain or SCD-specific studies limiting generalizability. Rigorous, disease-specific neuroimaging research is therefore needed.

Clinical implications and future directions

Emerging preclinical data, early reports on patients, and mechanistic studies in healthy volunteers provide cautious optimism for CBD as a therapeutic option in SCD, but robust evidence is required before clinical adoption. The inconsistent efficacy and side-effect burden associated with THC-containing cannabinoids highlight the need to investigate purified CBD.

CBD is unlikely to resolve all SCD-related complications, yet there is a credible prospect that specific subgroups of patients may derive meaningful therapeutic benefit. This will

require rigorously designed clinical and mechanistic studies focusing on pain processing and neuroinflammation, while accounting for disease heterogeneity and severity, age, sex, comorbidities, and prior opioid exposure. Rather than treating variability as noise, future research should adopt stratified, mechanism-informed approaches to identify those most likely to benefit.

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Contributions

AdK wrote the manuscript and designed the figures. MH critically reviewed the manuscript and designed the figures. KG critically reviewed the manuscript and figures. OK wrote the manuscript and designed the figures.

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