Cannabidiolic Acid (CBDa) and Nausea: Mechanisms, Evidence, and Clinical Considerations

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Executive Summary

This paper provides an overview of the potential therapeutic role of cannabidiolic acid (CBDa), a naturally occurring cannabinoid found in raw hemp and cannabis plants, for the management of nausea and vomiting.[1] Through its interactions with key biological pathways involved in serotonin signaling, inflammation, and the endocannabinoid system, CBDa represents a promising avenue of investigation for combating both acute and delayed emesis. This paper aims to contextualize current findings, outline the pharmacological mechanisms of CBDa, and highlight where further clinical research is needed.

Introduction

Nausea is a highly prevalent and commonly encountered symptom triggered by a broad spectrum of causes, including gastrointestinal disorders, central nervous system (CNS) conditions, psychiatric diseases, and medications such as cancer chemotherapy. Clinically defined as an unpleasant, painless, and subjective feeling that one will imminently vomit.[2] Although nausea and vomiting are frequently assumed to exist on a temporal continuum, severe nausea can present without emesis, and patients typically report that nausea feels worse, is more disabling, and lasts much longer than the physical act of vomiting. From an epidemiological standpoint, more than 50% of adults experience at least one episode of nausea over 12 months, resulting in a massive economic and psychosocial burden.[2]

Nausea Pathophysiology

The underlying pathophysiology of nausea is complex and encompasses interactions between changeable psychological states, the CNS, the autonomic nervous system (ANS), the endocrine system, and gastric myoelectrical activity. The onset of nausea is determined by a "dynamic threshold" that fluctuates by the minute. This threshold is influenced by an individual's inherent physiological factors interacting with psychological states such as expectation, adaptation, and anxiety.[2]

Nauseogenic stimuli originating from visceral, vestibular, and chemoreceptor trigger zone inputs are mediated by neurotransmitters such as serotonin, dopamine, histamine, and acetylcholine. Emetic agents, such as chemotherapy drugs in the bloodstream, are detected by chemosensitive receptors and relayed via the area postrema to the nucleus tractus solitarius (NTS) in the brainstem. Furthermore, higher cortical areas and the limbic system, including the amygdala, putamen, and insular cortex, play an important role in nausea.[2]

Physical symptoms preceding emesis, such as sweating, paleness, and tachycardia, are mediated by the autonomic nervous system. Increasing nausea severity is directly related to shifts characterized by decreased parasympathetic and increased sympathetic modulation. Normal gastric myoelectrical activity is often disrupted during nausea, resulting in dysrhythmias such as tachygastria (faster frequency) or bradygastria (slower frequency). Endocrine factors also play a role; for example, increases in vasopressin secretion precede emesis, and serum vasopressin levels positively correlate with the overall intensity of nausea.[2]

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[1] Formato M, Crescente G, Scognamiglio M, et al. (-)-Cannabidiolic Acid, a Still Overlooked Bioactive Compound: An Introductory Review and Preliminary Research. *Molecules.* 2020;25(11):2638. Published 2020 Jun 5. doi:10.3390/molecules25112638

[2] Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. *Ther Adv Gastroenterol.* 2016;9(1):98-112. doi:10.1177/1756283X15618131

The Role of the Endocannabinoid System in Nausea

The endocannabinoid system (ECS) is an extensive biological system that plays a critical role in maintaining homeostasis. The ECS consists of cannabinoid receptors, endogenous lipid ligands (endocannabinoids), and the enzymes responsible for their synthesis and degradation. It is heavily involved in the circuits that regulate the emetic reflex and nausea.[3] CB1 receptors are located within the "vomiting center" or the medulla and the area subpostrema of the NTS, where they modulate nauseogenic signaling.[2] Cannabinoids are also believed to modulate 5-HT3 receptor activation in nodose ganglia and suppress the release of substance P within the spinal cord. These are both important for delayed vomiting.[2,3]

Preclinical studies indicate that supplementing or boosting the endocannabinoid system with phytocannabinoids may help to manage conditions such as nausea and vomiting effectively. This is suggested to occur through mechanisms such as blocking the breakdown of the body's natural endocannabinoids, 2-AG and anandamide, by inhibiting the production of FAAH and MAGL, the enzymes responsible for their degradation.[4]

What is CBDa?

Cannabidiolic acid (CBDa) is one of the primary cannabinoids produced by cannabis plants, particularly fiber-type Cannabis sativa. It exists in the raw plant before decarboxylation, the process by which heat converts CBDa into CBD. Since it is typically found in unheated or minimally processed extracts, proper handling and formulation are necessary to preserve CBDa, which is relatively unstable and gradually decarboxylates over time.[1]

Mechanisms of Action

The ability of CBDa to relieve nausea is driven by its interaction with biological pathways involved in central nervous system signaling, inflammatory responses, and cellular stress.

5-5T1A Receptor Interaction

CBDa interacts potently with the 5-HT1A receptor, acting as a positive allosteric modulator, magnifying the body's natural serotonin response to suppress nausea.[5] Through activation of the 5-HT1A receptors within the dorsal raphe nucleus, signals in the brain are released to reduce the release of serotonin into the

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[3] Lu HC, Mackie K. Review of the Endocannabinoid System. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2020;6(6). doi:https://doi.org/10.1016/j.bpsc.2020.07.016

[4] Hermanson DJ, Gamble-George JC, Marnett LJ, Patel S. Substrate-selective COX-2 inhibition as a novel strategy for therapeutic endocannabinoid augmentation. *Trends Pharmacol Sci.* 2014;35(7):358-367. doi:10.1016/j.tips.2014.04.006

[5] Pertwee RG, Rock EM, Guenther K, et al. Cannabidiolic acid methyl ester, a stable synthetic analogue of cannabidiolic acid, can produce 5-HT1A receptor-mediated suppression of nausea and anxiety in rats. *Br J Pharmacol.* 2018;175(1):100-112. doi:10.1111/bph.14073

forebrain regions such as the interoceptive insular cortex (IIC).[6,7] High levels of serotonin within the IIC can trigger nausea. CBDa may effectively prevent this nausea-inducing spike of serotonin within the IIC, stopping nausea at its source.[7]

COX-2 Interaction

Preclinical research indicates that CBDa may target cyclooxygenase-2 (COX-2), an enzyme involved in inflammatory signaling. COX-2 levels are typically increased during immune activation and cellular stress, making it a significant target in inflammatory conditions. CBDa acts as a selective COX-2 inhibitor, dampening the expression of COX-2.[8,9]

PPAR Interaction

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent nuclear transcription factors that play a fundamental role in regulating gene expression related to energy homeostasis, lipid metabolism, and inflammation.[10,11] Recent research has identified CBDa as a dual agonist of PPARα and PPARγ. CBDa appears to act as a partial agonist at these receptors, effectively upregulating genes involved in fatty acid metabolism, such as CPT1a and ACOX1.[9]
Both systemic inflammation and metabolic dysregulation frequently accompany nausea-inducing clinical conditions such as cancer chemotherapy or neurodegenerative disorders.[9,10] CBDa's action across multiple PPAR pathways, which help combat systemic inflammation and metabolic dysregulation, may provide a more comprehensive therapeutic profile than its interaction with 5-HT1A.

Relevance to Nausea and Vomiting

Nausea and vomiting are highly distressing physiological reactions, particularly in patients with cancer. While current standard anti-emetic medications do effectively control vomiting, effective treatments for anticipatory nausea, a conditioned response to nauseating stimuli, are limited to behavioral interventions.[12] CBDa is highly relevant to this gap in care, as preclinical studies demonstrate its ability

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[6] Bolognini D, Rock EM, Cluny NL, et al. Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. *Br J Pharmacol.* 2013;168(6):1456-1470. doi:10.1111/bph.12043

[7] Rock EM, Limebeer CL, Pertwee RG, Mechoulam R, Parker LA. Therapeutic Potential of Cannabidiol, Cannabidiolic Acid, and Cannabidiolic Acid Methyl Ester as Treatments for Nausea and Vomiting. *Cannabis Cannabinoid Res.* 2021;6(4):266-274. doi:10.1089/can.2021.0041

[8] Takeda S, Misawa K, Yamamoto I, Watanabe K. Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metab Dispos.* 2008;36(9):1917-1921. doi:10.1124/dmd.108.020909

[9] Hirao-Suzuki M, Takayuki K, Takiguchi M, Peters JM, Takeda S. Cannabidiolic acid activates the expression of the PPARβ/δ target genes in MDA-MB-231 cells. *Archives of Biochemistry and Biophysics.* 2022;731:109428. doi:10.1016/j.abb.2022.109428

[10] D'Aniello E, Fellous T, Iannotti FA, et al. Identification and characterization of phytocannabinoids as novel dual PPARα/γ agonists by a computational and in vitro experimental approach. *Biochim Biophys Acta Gen Subj*. 2019;1863(3):586-597. doi:10.1016/j.bbagen.2019.01.002

[11] Sanjay, Sharma A, Lee HJ. Role of Phytoconstituents as PPAR Agonists: Implications for Neurodegenerative Disorders. *Biomedicines*. 2021;9(12):1914. Published 2021 Dec 14. doi:10.3390/biomedicines9121914

[12] Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. *Support Care Cancer.* 2011;19(10):1533-1538. doi:10.1007/s00520-010-0980-0

to effectively suppress both acute and anticipatory nausea.[13, 14]

Evidence Overview

Preclinical Evidence

Extensive preclinical animal studies demonstrate the potent anti-nausea and anti-emetic effects of CBDa. In animal studies using house musk shrews, CBDa reduces toxin-induced vomiting, including that induced by lithium chloride and chemotherapy drugs such as cisplatin. In addition, CBDa has demonstrated broad efficacy by suppressing motion-induced vomiting and does not cause emesis when administered on its own.[6]
In other rodent models of nausea, CBDa was found to suppress acute nausea and dramatically block anticipatory nausea. CBDa can achieve these therapeutic effects at very low doses compared to its decarboxylated counterpart, CBD.[9]

Clinical / Observational Insights

While there is preclinical evidence that establishes CBDa as an antiemetic, human trials targeting the anti-nausea effects of CBDa are still needed. However, the potential of CBDa demonstrated in validated animal models offers a compelling clinical rationale for prioritizing CBDa in future human studies.

Clinical Considerations

Preclinical data suggest a strong synergistic relationship between CBDa and standard antiemetics such as ondansetron. Using low doses of CBDa with these traditional antiemetics has been shown to enhance the suppression of nausea.[6] Additionally, combining lower doses of THC and CBDa has also been shown to be effective in reducing acute and anticipatory nausea.[11]
Unlike THC, CBDa is a non-psychotropic component of cannabis; when taken alone, it will not produce intoxicating effects, making it tolerable for a wider range of patients. The primary limitation of CBDa is its chemical instability, which causes decarboxylation to CBD when exposed to heat, light, and oxygen.

Conclusion

By targeting multiple underlying pathways, including 5-HT1A receptor activation, COX-2 inhibition, and PPAR agonism, CBDa may help combat motion-induced and treatment-resistant nausea. Although its chemical instability requires careful formulation, CBDa's ability to synergize with existing antiemetics and THC makes it a prime candidate for clinical investigation.

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[13] Rock EM, Limebeer CL, Navaratnam R, et al. A comparison of cannabidiolic acid with other treatments for anticipatory nausea using a rat model of contextually elicited conditioned gaping. *Psychopharmacology (Berl).* 2014;231(16):3207-3215. doi:10.1007/s00213-014-3498-1
[14] Rock EM, Connolly C, Limebeer CL, Parker LA. Effect of combined oral doses of Δ9-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models. *Psychopharmacology (Berl).* 2016;233(18):3353-3360. doi:10.1007/s00213-016-4378-7

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