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Review Article

The Role of the Endocannabinoid System in Neuroprotection: Mechanisms and Therapeutic Potential

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Abstract

The endocannabinoid system (ECS) regulates vital functions such as mood, immune response, and pain through cannabinoid receptors (CB1, CB2), endocannabinoids, and associated enzymes. In this discussion, we explore how endocannabinoids play a crucial role in neuroprotection, offering therapeutic potential for neurodegenerative diseases like Alzheimer's and Parkinson's through their anti-inflammatory, antioxidant, and neurogenic effects. Targeting the ECS with cannabinoids or enzyme inhibitors shows promise as a treatment strategy for these conditions.

Keywords: *Endocannabinoid System (ECS); Cannabinoid Receptors (CB1, CB2); Neuroprotection*

Introduction

The endocannabinoid system (ECS) is a sophisticated cell-signaling mechanism that is essential to preserving the body's homeostasis. found in the early nineties [1]. It has since been found to be crucial for controlling a variety of physiological functions, such as immunological response, mood, appetite, and pain [2,3].

Moreover, the ECS is a pervasive neuromodulatory system that regulates many physiological and cognitive functions in addition to being crucial to the growth of the central nervous system [4]. The system consists of endogenous cannabinoids, cannabinoid receptors, and enzymes that are responsible for the synthesis and breakdown of endocannabinoids [4].

Cannabinoid receptor CB1 and CB2 are the most extensively studied cannabinoid receptors, both of which are G protein-coupled receptors (GPCRs), They inhibit adenylyl cyclase and certain voltage-sensitive calcium channels, activate mitogen-activated protein (MAP) kinases and inwardly rectifying potassium channels (GIRKs), and recruit beta-arrestins, among other actions [4]. CB1 receptors are predominantly found in the central nervous system (CNS) [5] CB2 receptors are primarily located in peripheral tissues [6], especially within the immune system [6].

The body generates its own cannabinoids, called endocannabinoids, including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are the most well-known and can activate a wide variety of GPCRs, nuclear receptors, and ion channels [4].

Anandamide (AEA) was first discovered in the porcine brain [7] is often referred to as the "bliss molecule" due to its role in mood regulation and its association with feelings of well-being [8]. It primarily binds to CB1 receptors, influencing processes like pain sensation, mood, and appetite [8]. On the other hand, 2-AG, which is more plentiful in the body, regulates a range of processes, including immunological response and inflammation [9].

The processes of endocannabinoids production and breakdown are tightly regulated by specific enzymes [10]. Anandamide and 2-AG synthesis processes are regulated by N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL) respectively [11,12]. While the degradation processes are regulated by Fatty acid amide hydrolase (FAAH) for anandamide [13], and monoacylglycerol lipase (MAGL) for 2-AG [14]. This ensures that the signaling effects of endocannabinoids are short-lived, allowing for precise regulation of their activity.

The ECS acts as a control system, maintaining balance in different physiological processes [15,16]. When a disturbance occurs such as injury, stress, or infection the ECS is activated to restore homeostasis [17]. For instance, when experiencing pain or inflammation, endocannabinoids are produced as needed and engage with CB1 and CB2 receptors to decrease pain sensation and regulate the immune system [18,19].

Significance of neuroprotection and neurodegeneration

Neuroprotection refers to the strategies and mechanisms that protect the nervous system, particularly neurons, from injury or degeneration [20]. It plays a vital role in preventing or slowing the progression of neurodegenerative diseases [20].

Neurons are highly specialized cells with limited regenerative capacity. Once damaged or lost, neurons cannot be easily replaced [21]. neuroprotection attempts to stop the first damage to neurons In order to preserve neurons' functionality and stop the development of neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [22-24].

Moreover, neuroprotection slow Disease Progression thereby improving the quality of life for affected individuals [25].

Neuroprotection can further reduce the Impact of Neuro inflammation [26], a common feature of neurodegenerative diseases, where the immune system's response to injury or disease can exacerbate neuronal damage [27], reducing the overall burden of neuronal injury.

Moreover, by protecting neurons, neuroprotective therapies can help preserve cognitive and motor function [28], which are often, declined duo to neurodegenerative diseases severely affecting an individual's ability to perform daily tasks, allowing individuals to maintain independence for a longer period.

Endocannabinoids and neuroprotection

Anti-inflammatory effects

Neuro inflammation, a complex molecular process, is typically triggered by the brain's defense mechanisms to provide protection. However, this response can escalate into prolonged immune system activation, potentially leading to harmful clinical conditions [29]. Mast cells and microglia are the primary neuro-immune protectors in brain tissue, working with astrocytes to link distant immune signals to the central nervous system during inflammation. These cells detect harmful stimuli and produce chemokines and pro-inflammatory cytokines [30].

As people age, microglia become more sensitive to external triggers, leading to chronic, low-grade inflammation, a process known as "inflammaging" [31].

The endocannabinoid system is emerging as a promising therapeutic target for chronic neuro inflammation, with evidence suggesting that both synthetic and naturally occurring cannabinoids can modulate the pro-inflammatory response of microglia and potentially promote a shift towards an anti-inflammatory state. The activation of cannabinoid type two (CB2) receptors is proposed to be the key mechanism driving these effects [32].

Anti-oxidative properties

Redox imbalance can cause excessive ROS/RNS production, leading to oxidative tissue damage, a key factor in neurodegenerative diseases [33].

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in addition to their main function of regulating neurotransmission by activating cannabinoid receptors (CB1 and CB2), demonstrate noteworthy antioxidant characteristics that are especially pertinent for neuroprotection [34]. These endocannabinoids can directly neutralize reactive oxygen species (ROS), preventing oxidative damage that contributes to neurodegeneration [35]. Their chemical structure enables them to donate electrons to ROS, neutralizing these harmful molecules before they can damage cellular components like lipids, proteins, and DNA [35]. Furthermore, the antioxidant effects of anandamide and 2-AG extend beyond direct ROS scavenging; they also modulate the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which are crucial in the body's defense against oxidative stress, thereby enhance the brain's intrinsic antioxidant capacity, providing an additional layer of protection against oxidative damage [36].

Synaptic plasticity and neurogenesis

Endocannabinoids are crucial modulators of synaptic plasticity and neurogenesis, contributing significantly to overall brain plasticity [37]. They regulate synaptic plasticity by modulating neurotransmitter release, facilitating both long-term potentiation (LTP) and long-term depression (LTD), which are essential for learning and memory processes [38]. Moreover, eCBs have been shown to promote neurogenesis, particularly in the hippocampal dentate gyrus, by influencing neural progenitor cell proliferation, differentiation, and survival [38]. This neurogenic effect is crucial for maintaining cognitive function and adaptability in response to environmental changes and supporting cognitive flexibility and resilience throughout life.

Endocannabinoid-driven modulation of glutamate

By binding to presynaptic CB1 receptors, endocannabinoids inhibit glutamate release, maintaining a balanced excitatory-inhibitory environment and protecting neurons from excitotoxicity [39,40]. In conditions of neuro inflammation or neurodegeneration, where glutamate release can become dysregulated and contribute to neuronal injury, the endocannabinoid system's ability to modulate this process becomes particularly valuable [41].

Therapeutic potential of targeting the endocannabinoid system

Multiple physiological processes such as pain, appetite, mood and immune response are regulated by the endocannabinoid system, which makes it a promising target for therapeutic interventions [42]. Enzyme inhibitors or cannabinoids that alter the ECS have demonstrated promise in the treatment of diseases like anxiety, neurodegenerative illnesses, and chronic pain [43]. For instance, cannabinoids like THC and CBD have been studied for their analgesic properties in pain management, while inhibitors of endocannabinoid-degrading enzymes like FAAH are being explored to enhance endocannabinoid signaling [44]. Moreover, ECS is suggested to be used for treatment of diseases such as Alzheimer's and multiple sclerosis duo to its involvement in neuro inflammation [45].

Enzyme inhibitors (FAAH, MAGL)

Monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) are enzymes that, when inhibited, can help enhance the effects of endocannabinoids, offering potential neuroprotective benefits. FAAH inhibitors work by preventing the breakdown of anandamide,

a key endocannabinoid. By increasing anandamide levels, these inhibitors can help protect the brain from excitotoxicity and reduce neuro inflammation, which is particularly important in conditions like Alzheimer's disease [46]. Comparably, MAGL inhibitors stop 2-AG, another important endocannabinoid, from degrading. This increases its neuroprotective benefits, which include lowering inflammation and oxidative stress-two factors that are crucial in neurodegenerative illnesses like Parkinson's [47]. These enzyme inhibitors offer a targeted strategy to enhance the body's own endocannabinoid system, providing a novel avenue for neuroprotection [48].

Future Directions

The future of cannabinoid-based therapies is moving towards personalized medicine, where treatments are tailored to individual genetic profiles. Understanding genetic variations in cannabinoid receptors (CB1 and CB2) and enzymes involved in endocannabinoid metabolism can help predict patient responses, enhancing therapeutic outcomes and minimizing side effects [49]. This approach aligns with the trend towards precision medicine, aiming to effectively manage complex conditions like chronic pain, epilepsy, and neurodegenerative diseases by focusing on individual patient needs [50].

Drug combinations including cannabinoids have the potential of increased activity especially for neurodegenerative diseases. Such as using ECS modulators alongside antioxidants or anti-inflammatory drugs to tackle multiple aspects of brain damage [51]. Additionally, pairing ECS therapies with lifestyle changes like diet and exercise might enhance their protective effects, offering a well-rounded strategy for slowing disease progression [52]. As we learn more, these combination therapies are likely to play a big role in future treatments.

Conclusion

In conclusion, this research elucidates endocannabinoid system (ECS) role in neuroprotection, revealing that endocannabinoids, through their multiple systemic effects, contribute to safeguarding neurons and modulating the progression of neurodegenerative diseases such as Alzheimer and Parkinson's. These findings are therapeutically important because they indicate that using cannabinoids or enzyme inhibitors to target the ECS could be a potential strategy for creating medicines that effectively cure these diseases. Nonetheless, despite the promising potential, an urgent need for more detailed studies and clinical trials remains essential, in order to fully understand the therapeutic potential of the ECS. Ongoing and Continuing research in this area is essential to unlock the full benefits of ECS-targeted therapies and to transform these insights into practical and personalized medical interventions.

Bibliography

1. Battista N., *et al*. "The endocannabinoid system: an overview". *Frontiers in Behavioral Neuroscience* 6 (2012): 9.
2. Watkins BA. "Endocannabinoids, exercise, pain, and a path to health with aging". *Molecular Aspects of Medicine* 64 (2018): 68-78.
3. Alharthi NS. "Endocannabinoid system components: A crucial role in regulation of disease". *Journal of Advanced Pharmacy Education and Research* 12.3 (2022): 72-81.
4. Lu HC and K Mackie. "Review of the endocannabinoid system". *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 6.6 (2021): 607-615.
5. Svíženská I., *et al*. "Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures-a short review". *Pharmacology Biochemistry and Behavior* 90.4 (2008): 501-511.
6. Onaivi ES., *et al*. "Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain". *Annals of the New York Academy of Sciences* 1074.1 (2006): 514-536.
7. Devane WA., *et al*. "Isolation and structure of a brain constituent that binds to the cannabinoid receptor". *Science* 258.5090 (1992): 1946-1949.

8. Scherma M., *et al*. "Brain activity of anandamide: a rewarding bliss?" *Acta Pharmacologica Sinica* 40.3 (2019): 309-323.

9. Cabral GA., *et al*. "Endocannabinoids and the immune system in health and disease". *Endocannabinoids* 231 (2015): 185-211.

10. Basavarajappa BS. "Critical enzymes involved in endocannabinoid metabolism". *Protein and Peptide Letters* 14.3 (2007): 237-246.

11. Bisogno T. "Endogenous cannabinoids: structure and metabolism". *Journal of Neuroendocrinology* 20.1 (2008): 1-9.

12. Jain T., *et al*. "Diacylglycerol lipaseα (DAGLα) and DAGLβ cooperatively regulate the production of 2-arachidonoyl glycerol in autaptic hippocampal neurons". *Molecular Pharmacology* 84.2 (2013): 296-302.

13. Deutsch DG. "A personal retrospective: elevating anandamide (AEA) by targeting fatty acid amide hydrolase (FAAH) and the fatty acid binding proteins (FABPs)". *Frontiers in Pharmacology* 7 (2016): 370.

14. Pan B., *et al*. "Blockade of 2-AG hydrolysis by selective monoacylglycerol lipase inhibitor JZL184 enhances retrograde endocannabinoid signaling". *Journal of Pharmacology and Experimental Therapeutics* 331.2 (2009): 591-597.

15. Bermudez-Silva FJ., *et al*. "The role of the endocannabinoid system in the neuroendocrine regulation of energy balance". *Journal of Psychopharmacology* 26.1 (2012): 114-124.

16. Woods SC. "The endocannabinoid system: mechanisms behind metabolic homeostasis and imbalance". *The American Journal of Medicine* 120.2 (2007): S9-S17.

17. Lowe H., *et al*. "The endocannabinoid system: a potential target for the treatment of various diseases". *International Journal of Molecular Sciences* 22.17 (2021): 9472.

18. Donvito G., *et al*. "The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain". *Neuropsychopharmacology* 43.1 (2018): 52-79.

19. Bouchet CA and SL Ingram. "Cannabinoids in the descending pain modulatory circuit: Role in inflammation". *Pharmacology and Therapeutics* 209 (2020): 107495.

20. Mahalakshmi B., *et al*. "Possible neuroprotective mechanisms of physical exercise in neurodegeneration". *International Journal of Molecular Sciences* 21.16 (2020): 5895.

21. Fague L., *et al*. "The basic science of optic nerve regeneration". *Annals of Translational Medicine* 9.15 (2021): 1276.

22. Fumia A., *et al*. "Role of nutraceuticals on neurodegenerative diseases: Neuroprotective and immunomodulant activity". *Natural Product Research* 36.22 (2022): 5916-5933.

23. Evans JA., *et al*. "Neuroprotective effects and therapeutic potential of the citrus flavonoid hesperetin in neurodegenerative diseases". *Nutrients* 14.11 (2022): 2228.

24. Mohd Sairazi NS and K Sirajudeen. "Natural products and their bioactive compounds: neuroprotective potentials against neurodegenerative diseases". *Evidence-Based Complementary and Alternative Medicine* (2020): 6565396.

25. Krishnamurthy PT., *et al*. "Neuroprotective approaches to halt Parkinson's disease progression". *Neurochemistry International* 158 (2022): 105380.

26. Kempuraj D., *et al*. "Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma". *Biofactors* 47.2 (2021): 190-197.

27. Marogianni C., *et al*. "Neurodegeneration and inflammation-an interesting interplay in Parkinson's disease". *International Journal of Molecular Sciences* 21.22 (2020): 8421.

28. Kasindi, A., *et al*. "Glatiramer acetate immunomodulation: evidence of neuroprotection and cognitive preservation". *Cells* 11.9 (2022): 1578.

29. Rathod, S.S., *et al*. "Neuroinflammation in the central nervous system: Exploring the evolving influence of endocannabinoid system". *Biomedicines* 11.10 (2023): 2642.

30. D Skaper S. "Mast cell-glia dialogue in chronic pain and neuropathic pain: blood-brain barrier implications". *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)* 15.9 (2016): 1072-1078.

31. Frasca D., *et al*. "Aging, obesity, and inflammatory age-related diseases". *Frontiers in Immunology* 8 (2017): 1745.

32. Young AP and EM Denovan-Wright. "The dynamic role of microglia and the endocannabinoid system in neuroinflammation". *Frontiers in Pharmacology* 12 (2022): 806417.

33. Limongi D and S Baldelli. "Redox imbalance and viral infections in neurodegenerative diseases". *Oxidative Medicine and Cellular Longevity* (2016): 6547248.

34. Paloczi J., *et al*. "Neuroprotection in oxidative stress-related neurodegenerative diseases: role of endocannabinoid system modulation". *Antioxidants and Redox Signaling* 29.1 (2018): 75-108.

35. Hampson A., *et al*. "Cannabidiol and (−) Δ9-tetrahydrocannabinol are neuroprotective antioxidants". *Proceedings of the National Academy of Sciences* 95.14 (1998): 8268-8273.

36. Molina-Holgado E and F Molina-Holgado. "Mending the broken brain: neuroimmune interactions in neurogenesis". *Journal of Neurochemistry* 114.5 (2010): 1277-1290.

37. Chevaleyre V., *et al*. "Endocannabinoid-mediated synaptic plasticity in the CNS". *Annual Review of Neuroscience* 29.1 (2006): 37-76.

38. Galve-Roperh I., *et al*. "The endocannabinoid system and neurogenesis in health and disease". *The Neuroscientist* 13.2 (2007): 109-114.

39. Saluja I., *et al*. "X11α haploinsufficiency enhances Aβ amyloid deposition in Alzheimer's disease transgenic mice". *Neurobiology of Disease* 36.1 (2009): 162-168.

40. Zahid S., *et al*. "Phosphoproteome profiling of substantia nigra and cortex regions of Alzheimer's disease patients". *Journal of Neurochemistry* 121.6 (2012): 954-963.

41. Wang PY., *et al*. "Antitumor and immunomodulatory effects of polysaccharides from broken-spore of Ganoderma lucidum". *Frontiers in Pharmacology* 3 (2012): 135.

42. Lu HC and K Mackie. "An introduction to the endogenous cannabinoid system". *Biological Psychiatry* 79.7 (2016): 516-525.

43. Di Marzo V. "New approaches and challenges to targeting the endocannabinoid system". *Nature Reviews Drug Discovery* 17.9 (2018): 623-639.

44. Russo EB. "Cannabinoids in the management of difficult to treat pain". *Therapeutics and Clinical Risk Management* 4.1 (2008): 245-259.

45. Morales P and PH Reggio. "An update on non-CB1, non-CB2 cannabinoid related G-protein-coupled receptors". *Cannabis and Cannabinoid Research* 2.1 (2017): 265-273.

46. Blankman JL and BF Cravatt. "Chemical probes of endocannabinoid metabolism". *Pharmacological Reviews* 65.2 (2013): 849-871.

47. Nomura DK., *et al*. "Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation". *Science* 334.6057 (2011): 809-813.

48. Ahn K., *et al*. "Enzymatic pathways that regulate endocannabinoid signaling in the nervous system". *Chemical Reviews* 108.5 (2008): 1687-1707.

49. Hryhorowicz S., *et al*. "Pharmacogenetics of cannabinoids". *European Journal of Drug Metabolism and Pharmacokinetics* 43.1 (2018): 1-12.

50. Pisanti S., *et al*. "Cannabidiol: State of the art and new challenges for therapeutic applications". *Pharmacology and Therapeutics* 175 (2017): 133-150.

51. Fernández-Ruiz J., *et al*. "Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?" *British Journal of Clinical Pharmacology* 75.2 (2013): 323-333.

52. Cassano T., *et al*. "From *Cannabis sativa* to cannabidiol: Promising therapeutic candidate for the treatment of neurodegenerative diseases". *Frontiers in Pharmacology* 11 (2020): 124.

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