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Cannabinoid Receptor Activation Mitigates Hypertension *via* Glycolysis Inhibition in Microglia

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Abstract

Hypertension, characterized by elevated blood pressure, is a major risk factor for cardiovascular diseases and is often associated with neuroinflammation, contributing to the progression of vascular dysfunction. Recent studies have elucidated the therapeutic potential of cannabinoid receptor activation in mitigating hypertension-related neuroinflammation. Specifically, activation of the Cannabinoid Type 2 Receptor (CB2R) in microglia, the resident immune cells of the central nervous system, has emerged as a promising strategy for alleviating neuroinflammatory responses. This review highlights the molecular mechanisms underlying the anti-inflammatory effects of CB2R activation in microglia, focusing on the inhibition of aerobic glycolysis, a metabolic pathway implicated in the pathogenesis of neuroinflammation. By targeting key enzymes and transporters involved in aerobic glycolysis, CB2R activation effectively suppresses the pro-inflammatory phenotype of microglia, thereby attenuating neuroinflammation and mitigating the progression of hypertension. Furthermore, the therapeutic implications of CB2R activation extend beyond neuroinflammation to encompass broader cardiovascular effects, including vasodilation and cardio protection. Future research efforts aimed at delineating the specific molecular targets and cellular interactions involved in CB2R-mediated neuroprotection hold promise for the development of innovative therapeutic strategies for hypertension and related cardiovascular diseases.

Keywords: Cannabinoid receptor • Blood pressure • Microglia • Hypertension • Cardiovascular diseases

Introduction

Recent studies have shed light on the potential therapeutic effects of cannabinoid receptor activation in the context of hypertension. Specifically, the activation of the Cannabinoid Type 2 Receptor (CB2R) has emerged as a promising avenue for alleviating hypertension-related neuroinflammation. In a ground-breaking discovery, researchers have found that CB2R activation in microglia, the resident immune cells of the central nervous system, exerts profound anti-inflammatory effects through the inhibition of aerobic glycolysis. This metabolic pathway, characterized by the conversion of glucose to lactate even in the presence of oxygen, has been implicated in the pathogenesis of neuroinflammation associated with hypertension. By targeting aerobic glycolysis, CB2R activation effectively suppresses the pro-inflammatory responses of microglia, thus attenuating neuroinflammation and mitigating the progression of hypertension [1].

The intricate interplay between the endocannabinoid system and neuroinflammation has provided a mechanistic framework for understanding the therapeutic potential of CB2R activation in hypertension. Notably, CB2R activation has been shown to modulate the activity of microglia, which plays a pivotal role in orchestrating inflammatory responses within the central nervous system. Through various signalling pathways, CB2R activation inhibits the expression of pro-inflammatory cytokines and chemokines, dampening the inflammatory milieu associated with hypertension-induced neuroinflammation. Moreover, CB2R activation promotes the resolution of inflammation by enhancing the phagocytic clearance of cellular debris and apoptotic cells by microglia, thereby restoring tissue homeostasis and mitigating the detrimental effects of sustained inflammation on vascular function and blood pressure regulation.

Furthermore, the discovery of the role of aerobic glycolysis in mediating the anti-inflammatory effects of CB2R activation has provided novel insights into the metabolic regulation of neuroinflammation in hypertension. Aerobic glycolysis, also known as the Warburg effect, is a metabolic adaptation commonly observed in activated immune cells, including microglia. This metabolic reprogramming facilitates the rapid production of energy and biosynthetic intermediates to support the heightened metabolic demands of activated microglia during inflammation. However, dysregulated aerobic glycolysis exacerbates neuroinflammation by fueling the production of reactive oxygen species and inflammatory mediators. By targeting key enzymes and transporters involved in aerobic glycolysis, CB2R activation effectively suppresses the metabolic reprogramming of microglia, thereby curbing their inflammatory phenotype and mitigating hypertension-induced neuroinflammation [2].

Literature Review

Hypertension is a prevalent cardiovascular disorder associated with numerous complications, including neuroinflammation, which contributes to the progression of vascular dysfunction. In recent years, the therapeutic potential of cannabinoid receptor activation in mitigating hypertension-related neuroinflammation has garnered significant attention. This literature review aims to provide a comprehensive overview of the current understanding of cannabinoid receptor activation in the context of hypertension and neuroinflammation.

Cannabinoid receptors and neuroinflammation: Cannabinoid receptors, particularly the Cannabinoid Type 2 Receptor (CB2R), are widely expressed in the central nervous system, including microglia, the resident immune cells. Activation of CB2R has been shown to exert anti-inflammatory effects by modulating the activity of microglia and inhibiting the release of pro-inflammatory cytokines and chemokines. Preclinical studies have demonstrated that CB2R activation attenuates neuroinflammation and mitigates the progression of hypertension-induced central nervous system damage [3].

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Mechanisms of action: The anti-inflammatory effects of CB2R activation in hypertension-induced neuroinflammation are mediated, in part, by the inhibition of aerobic glycolysis, a metabolic pathway implicated in the pathogenesis of neuroinflammation. By targeting key enzymes and transporters involved in aerobic glycolysis, CB2R activation effectively suppresses the pro-inflammatory phenotype of microglia, thereby attenuating neuroinflammation and mitigating hypertension-associated complications.

Therapeutic implications: The elucidation of the molecular mechanisms underlying the anti-inflammatory effects of CB2R activation has important therapeutic implications for the management of hypertension and related cardiovascular diseases. Pharmacological interventions targeting the endocannabinoid system, particularly CB2R agonists, hold promise for alleviating neuroinflammation and improving vascular function in hypertensive individuals. Furthermore, lifestyle modifications and dietary interventions that modulate endocannabinoid tone and metabolic pathways may offer complementary approaches for the management of hypertension [4].

Discussion

Moreover, the discovery of the link between CB2R activation and the modulation of aerobic glycolysis in microglia sheds light on the intricate crosstalk between the endocannabinoid system, metabolism and inflammation in the context of hypertension. This multifaceted relationship underscores the potential for therapeutic interventions targeting metabolic pathways to alleviate neuroinflammation and ameliorate hypertension-associated complications. Importantly, the identification of specific molecular targets within the glycolytic pathway that mediate the anti-inflammatory effects of CB2R activation paves the way for the development of targeted pharmacological interventions with enhanced efficacy and specificity. Furthermore, the therapeutic implications of CB2R activation extend beyond neuroinflammation to encompass broader cardiovascular effects relevant to hypertension. Accumulating evidence suggests that CB2R activation exerts vasodilatory and cardioprotective effects, which contribute to the overall attenuation of hypertension and its associated cardiovascular risks [5].

By modulating endothelial function, vascular tone and cardiac remodeling, CB2R activation may mitigate the pathological changes observed in hypertensive individuals, thereby reducing the incidence of adverse cardiovascular events such as myocardial infarction and stroke. In addition to pharmacological interventions, lifestyle modifications and dietary interventions targeting the endocannabinoid system and metabolic pathways may offer complementary approaches for the management of hypertension. Emerging research suggests that dietary components such as omega-3 fatty acids and polyphenols, which have been shown to modulate endocannabinoid signaling and metabolic homeostasis, hold promise as adjunctive therapies for hypertension. Furthermore, lifestyle interventions such as exercise and stress reduction, which have been shown to enhance endocannabinoid tone and improve metabolic health, may complement pharmacological treatments in the holistic management of hypertension [6].

Conclusion

The discovery of the therapeutic potential of CB2R activation in mitigating hypertension-associated neuroinflammation through the inhibition of aerobic glycolysis in microglia represents a significant advancement in our understanding of the pathophysiology of hypertension. These findings not only highlight the complex interplay between the endocannabinoid system, metabolism and inflammation but also offer new insights into potential therapeutic strategies for hypertension and related cardiovascular diseases. Future research endeavors aimed at elucidating the molecular mechanisms underlying the cardio protective effects of CB2R activation and exploring synergistic approaches combining pharmacological interventions, lifestyle modifications and dietary interventions hold promise for advancing the field of hypertension therapeutics and improving clinical outcomes for affected individuals.

Acknowledgment

None.

Conflict of Interest

No conflict of interest.

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