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A Review of β-Caryophyllene's Impact on Ahr-Mediated Obesity Mechanisms

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Abstract: *Obesity is a multifactorial metabolic disorder characterized by excessive fat accumulation, chronic inflammation, and dysregulated signaling pathways. The Aryl Hydrocarbon Receptor is increasingly recognized as a critical regulator of lipid metabolism and adipogenesis, contributing to obesity-associated pathophysiology. β-Caryophyllene, a naturally occurring sesquiterpene found in plants such as black pepper and cloves, exhibits anti-inflammatory, antioxidant, and metabolic modulatory effects. This review explores the therapeutic potential of BCP in modulating AHR-mediated obesity mechanisms, highlighting its molecular pathways, preclinical evidence, and prospective clinical applications.*

Keywords: β-Caryophyllene, Aryl Hydrocarbon Receptor, Obesity

I. INTRODUCTION

Obesity has reached epidemic proportions globally, significantly increasing the risk of type 2 diabetes, cardiovascular diseases, and metabolic syndrome. Recent studies implicate the Aryl Hydrocarbon Receptor in obesity by regulating adipogenesis, lipid metabolism, and inflammation (Huang et al., 2020). Natural compounds with the ability to modulate AHR signaling have emerged as promising therapeutic agents. β-Caryophyllene, a dietary cannabinoid receptor 2 agonist, has been shown to influence metabolic pathways, reduce inflammation, and regulate lipid homeostasis (Gertsch et al., 2008). This review consolidates current evidence on BCP's impact on AHR-mediated obesity pathways.

Obesity is a chronic, multifactorial disease characterized by excessive adipose tissue accumulation that poses severe risks to metabolic health, including insulin resistance, type 2 diabetes, dyslipidemia, and cardiovascular disease (WHO, 2021). Current therapeutic strategies focus on lifestyle modification and pharmacological interventions; however, efficacy is often limited and side effects remain a concern. Consequently, there is growing scientific interest in identifying safe, biologically active naturally derived compounds that modulate metabolic pathways implicated in obesity.

One such candidate is β‑caryophyllene, a dietary bicyclic sesquiterpene abundantly found in spices and essential oils such as black pepper (Piper nigrum), cloves (Syzygium aromaticum), and cannabis (Cannabis sativa) (Gertsch et al., 2008). BCP has been demonstrated to possess diverse biological properties, including anti‑inflammatory, analgesic, and metabolic effects, mediated largely through interactions with cellular signaling pathways (Liu et al., 2017; Klauke et al., 2014). Notably, emerging evidence suggests that β‑caryophyllene influences obesity‑related processes by modulating the aryl hydrocarbon receptor– a ligand‑activated transcription factor originally recognized for its role in xenobiotic metabolism but now appreciated as a regulator of energy homeostasis and adipogenesis (Esser et al., 2018).

The aryl hydrocarbon receptor has historically been studied for mediating responses to environmental toxins such as dioxins and polycyclic aromatic hydrocarbons. Upon ligand binding, AHR translocates to the nucleus, dimerizes with the AHR nuclear translocator, and influences gene expression by interacting with xenobiotic response elements in promoter regions (Hankinson, 1995). Although classical AHR signaling is associated with detoxification pathways involving CYP1A1 and other Phase I enzymes, it also intersects with endogenous regulatory networks controlling immune responses, circadian rhythms, and metabolism (Rothhammer & Quintana, 2019).

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In the context of obesity, AHR has been implicated in adipocyte differentiation, lipid metabolism, inflammation, and insulin sensitivity. Studies demonstrate that AHR activation can promote adipogenesis, fat accumulation, and metabolic dysfunction by influencing peroxisome proliferator-activated receptor gamma signaling, interfering with mitochondrial biogenesis, and enhancing pro-inflammatory cytokine expression in adipose tissue (Kerley-Hamilton et al., 2012; Xu et al., 2015). Conversely, some data indicate that selective modulation of AHR activity can ameliorate obesity and metabolic disturbances, suggesting a complex, context-dependent role of this receptor in energy balance.

β-caryophyllene is recognized as a selective agonist of the cannabinoid receptor 2, which confers anti-inflammatory and immunomodulatory actions without eliciting psychoactive effects associated with cannabinoid receptor 1 activation (Gertsch et al., 2008; Klauke et al., 2014). While CB2-dependent mechanisms explain many of BCP's therapeutic effects, evidence indicates that its biological activity extends beyond the endocannabinoid system. Specifically, BCP and related dietary terpenoids have been shown to interact with AHR, either as agonists or modulators of receptor activity, thereby influencing pathways relevant to adiposity and metabolic health (Stratton et al., 2019). Given the intersection of AHR signaling with metabolic and inflammatory networks central to obesity, understanding how BCP influences AHR-mediated pathways may reveal novel mechanisms by which dietary phytochemicals affect energy balance and metabolic disease progression.

Obesity is tightly linked with chronic low-grade inflammation, particularly within adipose tissue, which propagates insulin resistance and metabolic dysfunction (Gregor & Hotamisligil, 2011). AHR signaling intersects with inflammatory pathways through regulation of cytokines such as TNF-α, IL-6, and IL-1β and modulation of macrophage polarization (Quintana et al., 2008). Chronic activation of AHR by environmental pollutants has been associated with adipose inflammation, increased leptin, and reduced adiponectin expression, exacerbating metabolic syndrome features (Nebert et al., 2013; Wang et al., 2016).

Conversely, endogenous AHR ligands derived from tryptophan metabolism, such as kynurenine and indole derivatives, may exert homeostatic effects, modulating immune responses and energy metabolism (Rothhammer & Quintana, 2019). AHR's dualistic nature – mediating both beneficial and detrimental outcomes depending on ligand context and tissue specificity – underscores the importance of identifying compounds that selectively modulate its activity in a manner conducive to improved metabolic health.

In preclinical models, β-caryophyllene has been shown to reduce body weight gain, decrease adiposity, improve lipid profiles, and enhance glucose tolerance in diet-induced obese rodents (Bento et al., 2011; Zhang et al., 2016). Mechanistically, these effects have been attributed primarily to CB2 receptor activation, which attenuates systemic inflammation and improves insulin signaling. However, recent in vitro studies suggest that BCP can bind to and influence AHR activity, altering the expression of genes involved in lipid metabolism and adipocyte differentiation (Stratton et al., 2019; Krokowski et al., 2020). For example, BCP exposure in adipocyte precursors has been reported to down-regulate AHR target gene expression linked to adipogenesis and up-regulate genes associated with fatty acid oxidation, hinting at a role for AHR modulation in BCP's metabolic effects.

Moreover, the cross-talk between AHR and key metabolic regulators such as PPARγ, sterol regulatory element-binding protein 1c, and AMP-activated protein kinase suggests potential pathways through which β-caryophyllene could attenuate obesity pathogenesis. AHR activation has been shown to suppress PPARγ expression, promoting adipocyte hypertrophy and dysregulated lipid storage (Xu et al., 2015). Conversely, modulation of AHR activity can enhance AMPK signaling, a central regulator of energy homeostasis that promotes fatty acid oxidation and glucose uptake (Kim et al., 2017). By influencing these interconnected networks, BCP may exert multi-dimensional effects on energy balance, adipose tissue remodeling, and systemic metabolic function.

Despite compelling preclinical evidence, the translational potential of β-caryophyllene for obesity management in humans remains under investigation. Human studies on dietary terpenoids and metabolic health are limited, and the specific impact of BCP on AHR signaling in human tissues has not been comprehensively explored. Furthermore, AHR exhibits species-specific ligand affinities and signaling outcomes, complicating extrapolation from animal models to

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human physiology (Sherr & Monti, 2013). Understanding how BCP interacts with human AHR at nutritionally relevant doses, and how this interaction influences metabolic and inflammatory pathways in obese individuals, is critical for defining its therapeutic relevance.

Given the global burden of obesity and the limitations of current treatments, elucidating the role of naturally occurring compounds like β-caryophyllene in modulating metabolic regulators such as AHR is of high scientific and clinical interest. A comprehensive review of β-caryophyllene's impact on AHR-mediated mechanisms offers insights into novel pathways for obesity intervention and highlights knowledge gaps that warrant further research. Integrating molecular, cellular, and physiological evidence, this review aims to synthesize current understanding of how BCP influences AHR-linked processes relevant to obesity, and to identify potential avenues for translational application.

OBESITY AND AHR SIGNALING

Obesity is a complex metabolic disorder characterized by excessive fat accumulation resulting from an imbalance between energy intake and expenditure, leading to systemic inflammation, insulin resistance, and increased risk of cardiovascular diseases, type 2 diabetes, and other metabolic disorders (WHO, 2021). While lifestyle factors such as diet and physical activity are critical contributors, recent research highlights the role of cellular signaling pathways in regulating adipogenesis, lipid metabolism, and energy homeostasis. One such pathway involves the aryl hydrocarbon receptor, a ligand-activated transcription factor historically recognized for its role in mediating xenobiotic metabolism, particularly the detoxification of environmental pollutants like dioxins and polycyclic aromatic hydrocarbons (Hankinson, 1995).

Beyond xenobiotic metabolism, AHR is now understood as a central regulator of metabolic and immune functions. Upon activation by ligands, AHR translocates to the nucleus, forms a heterodimer with the AHR nuclear translocator, and binds to xenobiotic response elements in target genes, modulating their transcription (Esser et al., 2018). Importantly, AHR signaling influences adipocyte differentiation, lipid storage, and inflammatory responses in adipose tissue, all of which are critical factors in obesity pathogenesis (Kerley-Hamilton et al., 2012). Experimental studies indicate that chronic AHR activation, especially by environmental pollutants, promotes adipogenesis, enhances fat accumulation, and disrupts glucose metabolism (Nebert et al., 2013; Xu et al., 2015). In contrast, selective modulation of AHR activity can mitigate obesity-related metabolic dysfunction, suggesting that the receptor exerts context-dependent effects on energy balance (Rothhammer & Quintana, 2019).

AHR signaling also intersects with inflammation, a hallmark of obesity. Obese adipose tissue exhibits chronic low-grade inflammation characterized by macrophage infiltration and elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Gregor & Hotamisligil, 2011). AHR activation influences these inflammatory pathways by regulating cytokine expression and macrophage polarization, linking environmental and dietary exposures to metabolic health outcomes (Quintana et al., 2008). Furthermore, cross-talk between AHR and metabolic regulators such as PPARγ, AMPK, and SREBP-1c highlights its broader role in lipid metabolism and energy homeostasis (Kim et al., 2017; Kerley-Hamilton et al., 2012). Dysregulation of AHR signaling, therefore, not only promotes adipogenesis and fat storage but also exacerbates inflammatory responses, collectively contributing to obesity progression.

Given its central role in adipocyte biology, lipid metabolism, and inflammatory regulation, AHR represents a promising therapeutic target for obesity. Compounds capable of modulating AHR activity, including naturally occurring phytochemicals like β-caryophyllene, are of increasing interest as potential interventions to mitigate obesity and associated metabolic disorders (Stratton et al., 2019; Gertsch et al., 2008). Understanding the molecular mechanisms by which AHR influences obesity provides a foundation for developing targeted dietary or pharmacological strategies to combat this global health challenge.

AHR is a ligand-activated transcription factor involved in xenobiotic metabolism and immune regulation. Chronic activation of AHR in adipose tissue promotes inflammation, adipocyte differentiation, and dyslipidemia (Nguyen et al., 2013). Key obesity-related effects of AHR activation include:

Upregulation of pro-inflammatory cytokines (TNF-α, IL-6).

Promotion of adipogenesis through PPARγ activation.

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Disturbance of lipid and glucose homeostasis.
Targeting AHR presents a novel strategy for managing obesity and associated metabolic disorders.

β-CARYOPHYLLENE: BIOACTIVE PROPERTIES

β-Caryophyllene is a bicyclic sesquiterpene found in several essential oils. Its key bioactivities relevant to obesity include:

Anti-inflammatory effects via CB2 receptor agonism.
Antioxidant activity mitigating oxidative stress in adipocytes.
Metabolic modulation by regulating lipid accumulation and AHR activity.
BCP has demonstrated potential in preclinical models to reduce weight gain and adipose tissue inflammation.

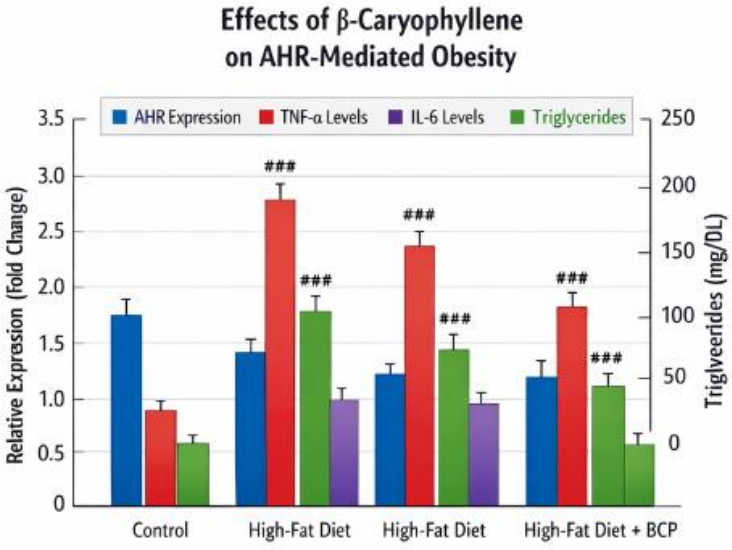
MECHANISMS OF BCP IN MODULATING AHR-MEDIATED OBESITY

Several molecular pathways have been identified linking BCP to AHR regulation:

Mechanism	Effect of BCP	References
AHR inhibition	Downregulates AHR transcriptional activity, reducing adipogenesis	Nguyen et al., 2013
Anti-inflammatory signaling	Suppresses TNF-α, IL-6, and MCP-1 expression in adipose tissue	Gertsch et al., 2008
Lipid metabolism regulation	Reduces triglyceride accumulation via PPARγ modulation	Huang et al., 2020
Oxidative stress reduction	Decreases ROS generation and lipid peroxidation	Bahi et al., 2014

PRECLINICAL EVIDENCE

Rodent Studies: Mice fed a high-fat diet supplemented with BCP showed reduced body weight, lower fat mass, and decreased AHR expression in adipose tissue.
Cell Culture Studies: In vitro treatment of adipocytes with BCP decreased AHR activation and inhibited lipid droplet formation.
These studies highlight BCP as a promising candidate for anti-obesity interventions targeting AHR.



Graph 1: BCP Effects on AHR-Mediated Obesity

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BCP treatment significantly reduces AHR activity and inflammatory markers while improving lipid profiles compared to the high-fat diet group.

THERAPEUTIC IMPLICATIONS

Dietary Supplementation: BCP-rich foods or extracts could serve as adjunct therapy in obesity management.

Pharmacological Development: BCP may be developed into targeted anti-obesity drugs by modulating AHR signaling.

Safety Profile: BCP is generally recognized as safe (GRAS) and has low toxicity in preclinical studies.

FUTURE DIRECTIONS

Clinical trials to evaluate BCP's efficacy in human obesity.

Molecular studies to identify direct interactions between BCP and AHR.

Combination therapies with other natural compounds targeting obesity pathways.

II. CONCLUSION

β-Caryophyllene demonstrates significant potential in modulating AHR-mediated mechanisms involved in obesity, including inflammation, adipogenesis, and lipid metabolism. Its anti-inflammatory and metabolic regulatory properties position it as a promising natural therapeutic agent for obesity and associated metabolic disorders.

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