

Review Article

# Endogenous cannabinoids may regulate chronic inflammation in aspirin-exacerbated respiratory disease

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## KEYWORDS

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Endogenous cannabinoid;  
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Eicosanoids;  
Prostaglandins

**Abstract** Aspirin-exacerbated respiratory disease (AERD) is characterized by the triad of chronic rhinosinusitis with nasal polyposis, adult-onset asthma and non-IgE mediated reactions to aspirin and other cyclooxygenase-1 (COX-1) inhibitors. Patients with AERD are dependent on COX-1 activity to maintain production of prostaglandin (PG) species, such as PGE<sub>2</sub>, which maintain physiologic levels of inflammation and limit the production of pro-inflammatory cysteinyl leukotrienes. The endogenous cannabinoid system is a family of immunomodulatory lipids and their innate g-protein coupled receptors that are closely related to arachidonic acid and may modulate inflammation via several pathways, including the direct production of metabolically active prostaglandin glycerol-esters. A recent pilot study has identified the significant up-regulation of the peripherally expressed, type-2 cannabinoid receptor (CB<sub>2</sub>) in AERD nasal polyps versus control tissues from patients with either allergic fungal rhinosinusitis or no history of chronic sinonasal inflammation. These early findings suggest the involvement of increased endogenous cannabinoid activity in prostaglandin deficient states such as AERD. Future study is needed to explore the significance of these findings, with specific investigation of the impact of CB<sub>2</sub> activation on markers of airway inflammation, as well as the potential to measure CB<sub>2</sub> expression as a screening biomarker for the evaluation of unrecognized disease. Copyright © 2020 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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## Introduction

Dysregulated prostaglandin synthesis is associated with chronic airway inflammation in AERD. Metabolism of prostaglandin substrates, such as arachidonic acid, are carefully balanced to control levels of inflammation. In AERD, however, arachidonic acid is shunted towards the pro-inflammatory 5-lipoxygenase (5-LO) pathway.<sup>1</sup> This shunting increases the production of inflammatory cysteinyl leukotrienes both at rest and following aspirin exposure, a finding which correlates with severity of disease.<sup>2,3</sup> Decreased expression of prostaglandin E2 (PGE2) receptors coupled with increased 5-LO further increases reliance on prostaglandin production and potentially explains the failure of leukotriene modifying drugs to control airway inflammation.<sup>4</sup> Prostaglandin metabolic pathways therefore represent an important target for drug discovery.

Endogenous cannabinoids (endocannabinoids) may impact airway inflammation in AERD by directly producing prostaglandins and regulating mediators of airway inflammation.<sup>5,6</sup> The endocannabinoid 2-arachidonoylglycerol (2-AG) is metabolized by either cyclooxygenase-2 (COX-2) into physiologically-active prostaglandin glycerol-esters, or fatty acid amid hydrolase into arachidonic acid (Fig. 1). Additionally, activation of type-2 cannabinoid (CB2) receptors on mast and other inflammatory cells decreases Th2 cytokine profiles, leukotriene synthesis and leukocyte migration, all features associated with AERD.<sup>7</sup>

## Cannabinoid biomarkers

The inability to identify patients with suspected AERD is a significant limitation of current practice. In fact, the gold standard to identify AERD, diagnostic aspirin challenge, is poorly utilized due to limited availability of specialized

providers and concerns of adverse reactions to the procedure.<sup>8</sup> This is a critical barrier to patient care, as up to 42% of subjects with asthma and nasal polyps fail to identify comorbid aspirin sensitivity.<sup>9</sup> These patients continue to be undiagnosed and inadequately treated until experiencing a life-threatening reaction to over the counter NSAIDs. New biomarkers are desperately needed to advance patient care.

Recent study has described the increased transcription of the CB2 receptor gene *CNR2* in AERD nasal polyp epithelium.<sup>10</sup> *CNR2* transcription was prospectively evaluated from nasal polyps of patients with AERD, allergic fungal rhinosinusitis (AFRS), or uninflamed mucosa from control patients undergoing a transphenoidal approach to the sella for the resection of nonfunctional pituitary adenomas. Findings included a >5-fold increase in *CNR2* among AERD patients versus either AFRS or control, a novel finding that is independent of tissue inflammation. This preliminary finding serves as a foundation to advance understanding of endocannabinoid function in airway disease, including the potential to measure expression of receptors as novel screening biomarkers prior to diagnostic aspirin challenge.

## Prostaglandin precursors

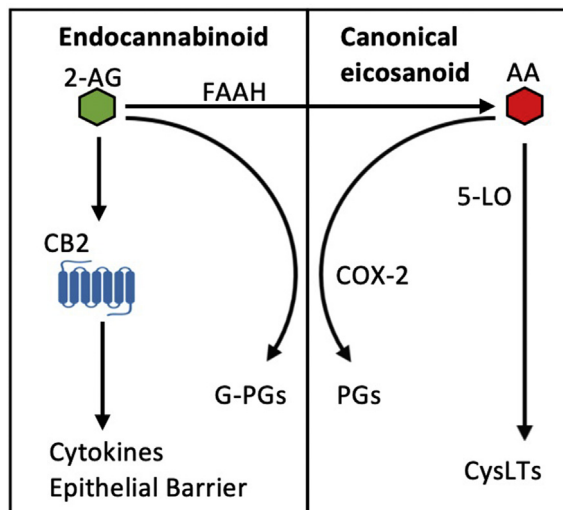
High-dose aspirin desensitization therapy is the only targeted intervention for the treatment of AERD.<sup>1</sup> While 80% of patients demonstrate improvement in respiratory symptoms, the mechanisms for this effect are incompletely understood. Following high-dose aspirin therapy, there is paradoxical decrease in PGE2 urinary metabolites.<sup>11</sup> We hypothesize that in AERD there is increased utilization of endogenous cannabinoids as prostaglandin substrates both at baseline and following aspirin desensitization. This substrate switching model from arachidonic acid is supported by a recent study identifying endocannabinoids as an alternative source of physiologically active prostaglandin glycerol-esters (Fig. 1).<sup>12</sup> Additional study is needed to evaluate the hypothesis that endocannabinoid activity is increased in AERD as a compensatory mechanism to increase prostaglandin production in the setting of decreased COX-2 activity.

## Conclusions

The endogenous cannabinoid system is a family of immunomodulatory lipids and their innate g-protein coupled receptors that are closely related to arachidonic acid. Recent study has identified significant up-regulation of peripheral CB2 receptors in AERD. These early findings suggest the association of increased endocannabinoid activity in prostaglandin deficient states such as AERD. Future study is needed to explore the significance of these findings, with specific investigation of CB2 transcription as a novel biomarker for unrecognized disease.

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**Fig. 1** Endogenous cannabinoids represent an alternative source of physiologically active prostaglandins. 2-AG: 2-Arachidonoylglycerol; 5-LO: 5-lipoxygenase; AA: Arachidonic acid; CB2: type-2 cannabinoid receptor; FAAH: fatty acid amid hydrolase; G-PGs: Prostaglandin glycerol-esters; CysLTs: Cysteinyl leukotrienes; PGs: Prostaglandins.

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## Conflicts of Interest

None

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