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Review

Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2

Emily C. Graff[a,b], Han Fang[a], Desiree Wanders[c], Robert L. Judd[a,*]

[a] Department of Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, Auburn, AL, United States
[b] Department of Pathobiology, College of Veterinary Medicine, Auburn University, Auburn, AL, United States
[c] Department of Nutrition, Georgia State University, Atlanta, GA, United States

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ABSTRACT

The hydroxycarboxylic acid receptors (HCA_{1-3}) are a family of G-protein-coupled receptors that are critical for sensing endogenous intermediates of metabolism. All three receptors are predominantly expressed on adipocytes and mediate anti-lipolytic effects. In addition to adipocytes, HCA_2 is highly expressed on immune cells, including macrophages, monocytes, neutrophils and dermal dendritic cells, among other cell types. The endogenous ligand for HCA_2 is beta-hydroxybutyrate (β-OHB), a ketone body produced by the liver through β-oxidation when an individual is in a negative energy balance. Recent studies demonstrate that HCA_2 mediates profound anti-inflammatory effects in a variety of tissues, indicating that HCA_2 may be an important therapeutic target for treating inflammatory disease processes. This review summarizes the roles of HCA_2 on inflammation in a number of tissues and clinical states.

1. Introduction

The hydroxycarboxylic acid receptors (HCA_{1-3}) are a family of G-protein-coupled receptors that recognize endogenous intermediates of metabolism and are critical for nutrient sensing. The endogenous ligand for HCA_1, formerly known as GPR81, is lactate, an energy intermediate produced by cells in states of anaerobic energy metabolism. The endogenous ligand for HCA_2, formerly known as GPR109a, is beta-hydroxybutyrate (β-OHB), a ketone body produced by the liver through β-oxidation when an individual is in a negative energy balance. HCA_3, formerly known as GPR109b, is only

Abbreviations: ABCG1, ATP-binding cassette sub-family G member 1; β-OHB, beta-hydroxybutyrate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; EC_{50}, half maximal effective concentration; FAE, fumaric acid esters; G_i, G-inhibitory; GPR, G-protein coupled receptor; HCA, hydroxycarboxylic acid; HDL, high-density lipoprotein; HSL, hormone sensitive lipase; ICAM, intracellular adhesion molecule; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL, interleukin; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein one; MMF, monomethyl fumarate; NEFA, non-esterified fatty acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family, pyrin domain containing 3; PGD_2, Prostaglandin D_2; PGE_2, Prostaglandin E_2; PKA, protein kinase A; SCFA, short-chain fatty acid; siRNA, silencing ribonucleic acid; T2DM, type 2 diabetes mellitus; TGFβ, transforming growth factor β; TLR, Toll-like receptor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule one; VLA, very late antigen.

* *Corresponding author at:* Boshell Diabetes and Metabolic Diseases Research Program, Department of Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, 219 Greene Hall, Auburn, AL, 36849, United States. Tel.: +1 334 844 5416; fax: +1 334 844 5388.
E-mail address: juddrob@auburn.edu (R.L. Judd).

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found in higher primates and is activated by 3-hydroxyoctanoate, a ketone body intermediate produced by skeletal muscle [1–3]. All three receptors are predominantly expressed on adipocytes, where they function to inhibit lipolysis. However, more recent studies involving the HCA_2 receptor demonstrate that it has profound anti-inflammatory properties as well [4,5]. This review summarizes the physiological and pathological roles of the HCA_2 receptor in inflammation in various tissues and clinical states.

2. HCA_2 Receptor

HCA_2 is a G_i protein-coupled receptor predominantly expressed on adipocytes (white and brown) and immune cells, including macrophages, monocytes, neutrophils and dermal dendritic cells, but not lymphocytes [6–12]. HCA_2 is also present in retinal pigmented and colonic epithelial cells, keratinocytes, microglia, and normal mammary tissue [13–16]. Although a number of studies report that the receptor is not expressed in the liver [9–11], a more recent study demonstrated low basal levels of HCA_2 in primary murine hepatocytes with expression being induced after exposure to inflammatory stimuli [17]. When compared across tissues, relative gene expression is highest in abdominal and epididymal white adipose tissue followed closely by subcutaneous white adipose tissue and the spleen, and lesser expression in lung and lymph node [18,19]. In these studies, minimal relative gene expression was also noted in the heart, liver, jejunum, kidney, ovary, testicle, pancreas, brain, and embryo [18,19]. Distribution of receptor expression appears to be fairly consistent among species [18].

It is believed that the primary role of HCA_2 on adipocytes is to inhibit lipolysis. Activation of HCA_2 on adipocytes prompts inhibition of adenylate cyclase activity, reduced cAMP levels, reduced protein kinase A (PKA) activity, and a rapid reduction in the activity of the lipolytic enzyme, hormone sensitive lipase (HSL) [10,20,21]. This triggers a rapid reduction in lipolysis and decreased release of non-esterified fatty acids (NEFAs) from the adipocyte.

Endogenous ligands for HCA_2 include the ketone body, β-OHB and butyrate, both of which serve as nutrient sources for cells under various physiological conditions [22,23]. β-OHB is produced in the liver through beta-oxidation of fatty acids and serves as an alternative fuel source for non-neuronal cells during times of starvation or negative energy balance. In 1968, ketones were first described as inhibitors of lipolysis on adipocytes in order to moderate fat breakdown and conserve glucose in times of starvation [24]. Nearly 40 years later, it was determined that this critical survival event was mediated by β-OHB activation of HCA_2 [23]. The EC_{50} for stimulation of HCA_2 by β-OHB is approximately 0.7 mmol/L, which are levels obtained in human serum after 2–3 days of fasting or upon administration of a ketogenic diet [23]. This negative feedback of β-OHB via HCA_2 promotes efficient utilization of fat energy stores and prevents the development of ketoacidosis [25,26].

Butyrate is a short-chain fatty acid (SCFA) produced by bacterial fermentation of dietary fiber in the colon [27]. In addition to serving as an important fuel source for colonic epithelial cells, butyrate is associated with many beneficial metabolic effects, including improved insulin sensitivity and increased energy expenditure in mice fed a high-fat diet [28,29]. These beneficial metabolic effects along with additional anti-inflammatory properties may be due to butyrate-mediated activation of the HCA_2 receptor on colonic epithelial cells [30].

In addition to endogenous ligands, there are several pharmacologic ligands for HCA_2 [26,31]. The oldest and most commonly utilized pharmacologic ligand is the anti-atherogenic drug niacin, also known as vitamin B3 and nicotinic acid. The pharmacologic effects of niacin were first discovered in 1955 by Dr. Rudolf Altschul, when he observed that consuming pharmacologic doses of niacin (3000 mg/day; compared to 15–20 mg/day necessary for vitamin properties of niacin) resulted in profound reductions in serum triglyceride and cholesterol concentrations [32]. However, it was not until 2003 that activation of HCA_2 was identified as being responsible for the anti-lipolytic properties of niacin [9–11]. Unfortunately, these doses of niacin resulted in the unwanted side effect of cutaneous flushing owing to HCA_2 receptor activation on keratinocytes and dermal dendritic cells [6]. Other exogenous ligands for HCA_2 are fumaric acid esters (FAE), including dimethyl fumarate and its metabolite, monomethyl fumarate (MMF). In 2008, a screen of 1500 low molecular weight carboxylic acids revealed that MMF was a potent and selective HCA_2 agonist [8]. Similarly to niacin, treatment with MMF results in the undesirable side effect of cutaneous flushing. The mechanisms responsible for the cutaneous flushing for niacin and MMF are activation of HCA_2 and subsequent formation of prostaglandin D_2 (PGD_2) and E_2 (PGE_2) [6].

While there has been much attention given to the anti-lipolytic properties of HCA_2, activation by endogenous and exogenous ligands has also been associated with anti-inflammatory effects in numerous disease states. In particular, studies report that niacin has the ability to reduce inflammation in atherosclerosis [5], obesity [4], sepsis [33], diabetic retinopathy [14] and renal disease [34] (Fig. 1). In the autoimmune skin condition psoriasis, MMF has been an important part of therapy for many years due to its anti-inflammatory properties [8]. Dimethyl fumarate is used for the immune-modulating treatment of psoriasis and multiple sclerosis [35]. Additional studies demonstrate anti-inflammatory effects of endogenous HCA_2 agonists, including butyrate and β-OHB [29,36,37]. While some of the beneficial effects of these HCA_2 ligands may be independent of receptor activation [37], there are numerous studies in various tissues and clinical conditions that demonstrate a clear receptor-mediated process [4,5,38,39].

3. Atherosclerosis

Atherosclerosis is a major cause of morbidity and mortality in developed countries worldwide. This disease is characterized as a slow, progressive accumulation and oxidation of apolipoproteins within the arterial wall [40]. Inflammation has been identified as a common underlying factor during all phases of the atherosclerotic process, including plaque initiation and progression [40]. The main feature of inflammation in atherosclerosis development is the infiltration of circulating monocytes into the arterial intima and subsequent