Trends in Endocrinology & Metabolism

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Review

Hydroxy-Carboxylic Acid Receptor Actions in Metabolism

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Lactic acid, the ketone body 3-hydroxy-butyric acid, also known as β-hydroxybutyrate, and the β-oxidation intermediate 3-hydroxy-octanoic acid are hydroxy-carboxylic acids (HCAs) that serve as intermediates of energy metabolism. However, they also regulate cellular functions, in part by directly activating the G protein-coupled receptors HCA_1/GPR81, HCA_2/GPR109A, and HCA_3/GPR109B. During the past decade, it has become clear that HCA receptors help to maintain homeostasis under changing metabolic and dietary conditions, by controlling metabolic, immune, and other body functions. Work based on genetic mouse models and synthetic ligands of HCA receptors has, in addition, shown that members of this receptor family can serve as targets for the prevention and therapy of diseases such as metabolic and inflammatory disorders.

Trends

Lactate activates HCA_1 on adipocytes in an autocrine manner. It inhibits lipolysis and thereby promotes anabolic effects. Blockade of HCA_1 may prevent and treat obesity.

HCA_2 and HCA_3 regulate adipocyte lipolysis and immune functions under conditions of increased FFA formation through lipolysis (e.g., during fasting). HCA_2 agonists acting mainly through the receptor on immune cells exert antiatherogenic and anti-inflammatory effects.

HCA_2 is a receptor for butyrate and mediates some of the beneficial effects of short-chain fatty acids produced by gut microbiota.

Introduction

Many nutrients and intermediates of energy metabolism are not only carriers of energy but also function as signaling molecules which modulate metabolic, immune, and other functions in the mammalian organism by activating specific receptors. While nuclear receptors have long been known to play important roles in mediating effects of metabolites [1,2], more recently various G protein-coupled receptors have also been shown to be activated by metabolic intermediates [3]. Prominent examples are the hydroxy-carboxylic acid (HCA) receptors. The HCA receptor family consists of three members, HCA_1, HCA_2, and HCA_3, also known as GPR81, GPR109A, and GPR109B, respectively, which are encoded by closely related genes [4]. The physiological ligands of HCA receptors are key metabolic intermediates whose local and systemic levels reflect particular metabolic states. Lactic acid, the end product of glycolysis, activates HCA_1, whereas the ketone body 3-hydroxy-butyric acid [β-hydroxybutyrate (β-HB)] and the β-oxidation intermediate 3-hydroxy-octanoic acid activate HCA_2 and HCA_3, respectively. In addition, HCA_2 is also activated by butyric acid. HCA receptors have relatively low affinities for their natural ligands, however, in some cases, synthetic ligands with increased affinity have been developed [4]. In addition, drugs such as nicotinic acid and dimethyl fumarate (DMF) have been shown to exert at least part of their pharmacological activity through the receptor HCA_2 [4–6]. The pharmacological properties of HCA receptors have recently been summarized by several reviews [4,7]. This review will focus on the physiological and pathophysiological functions, as well as on the therapeutic potential of this receptor family.

General Properties of HCA Receptors

The genes encoding the three HCA receptors are located next to each other on human chromosome 12 and mouse chromosome 5. HCA_1 is the phylogenetically oldest receptor, found already in fish [8]. By contrast, functionally active HCA_2 receptors appear to be restricted to mammals, and the HCA_3 receptor has only been found in higher primates [9]. Consistent with

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Table 1. HCA Receptors: Ligands and Expression Patterns

Natural ligand (EC_{50} in μM)	Receptor	Alias	Other ligands (selection; EC_{50} in μM)	Expression	Refs
Lactate (1300–4800)	HCA_1	GPR81	3,5-Dihydroxy-benzoic acid (190)	Adipocytes, gastric ghrelin cells, low levels in liver, kidney, skeletal muscle	[10,11,13, 92,93]
3-Hydroxy-butyrate (ketone body) (800) Butyrate (700–1600)	HCA_2	GPR109a HM74a, PUMA-G, NIACR1	Nicotinic acid (0.06–0.25) Acifran (2.1) Acipimox (2.6–6), monomethyl-fumarate (9.4) SCH900271 (0.002) MK-6892 (0.016) MK-1903 (0.013) GSK256073 (0.032)	Adipocytes, monocytes, macrophages, neutrophils, epidermal Langerhans cells, keratinocytes, intestinal epithelial cells, retinal pigment epithelium	[1,5,6, 14–16,23, 42,47,94–97]
3-Hydroxy-octanoic acid (8)	HCA_3	GPR109b HM74, NIACR2	Aromatic (-amino) acids Acifran (20) SCH900271 (0.096) compound 60 (0.003)	Adipocytes, immune cells, intestinal epithelium	[12,15,16, 24,28,94, 98,99]

the close genetic relationship of the genes encoding the three receptors, their main physiological ligands also show structural similarity, as they are all hydroxylated carboxylic acids. With regard to their downstream signaling, all HCA receptors are coupled to G_i-type G proteins [10–16].

The lactic acid receptor HCA_1 is primarily expressed in white and brown adipocytes [11,12,17,18] (Table 1). Only relatively low expression levels of HCA_1 have been described in several other tissues [16,19], and it is not clear whether this is due to the presence of adipocytes in these tissues or whether it reflects expression by other resident cell types. In contrast to HCA_1, HCA_2 and HCA_3 are more widely expressed (Table 1). HCA_2 also shows relatively high expression in white and brown adipocytes [14–16]. In addition, HCA_2 is expressed by immune cells including neutrophils, macrophages, and epidermal Langerhans cells, but not in lymphocytes [20–23]. Several types of epithelial cells including intestinal epithelial cells, retinal pigment epithelial cells, as well as keratinocytes also express HCA_2 [5,6,23–26]. HCA_3 is only expressed in higher primates, and its expression has not been studied in-depth. However, HCA_3 appears to be present in most tissues which also express HCA_2, including adipocytes, immune cells such as neutrophils, monocytes, and macrophages, as well as in intestinal epithelial cells [14,16,24,27–30].

HCA Receptors in the Adipose Tissue

All three HCA receptors are highly expressed in white and brown adipocytes. Expressions of HCA_1 and HCA_2 have been shown to increase during differentiation of adipocytes from preadipocytes as well as after activation of peroxisome proliferator-activated receptor-gamma [11,17,18]. Both high-fat diet (HFD) feeding and exposure to various inflammatory stimuli result in decreased expression of HCA_1 in the adipose tissue [31,32]. While HCA_2 expression in the adipose tissue is also decreased after HFD feeding, inflammatory stimuli increase expression of HCA_2 [20,31].