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Review Paper

Fatty and hydroxycarboxylic acid receptors: The missing link of immune response and metabolism in cattle

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ABSTRACT

Fatty and hydroxycarboxylic acids are one of the main intermediates of energy metabolism in ruminants and critical in the milk production of cattle. High production demands on a dairy farm can induce nutritional imbalances and metabolism disorders, which have been widely associated with the onset of sterile inflammatory processes and increased susceptibility to infections. The literature suggests that short-chain fatty acids (SCFA), long-chain fatty acids (LCFA) and hydroxycarboxylic acids are relevant modulators of the host innate inflammatory response. For instance, increased SCFA and lactate levels are associated with subacute ruminal acidosis (SARA) and the activation of pro-inflammatory processes mediated by diverse leukocyte and vascular endothelial cells. As such, free LCFA and the ketone body β-hydroxybutyrate are significantly increased in the plasma 1–2 weeks postpartum, coinciding with the time period in which cows are more susceptible to acquiring infectious diseases that the host innate immune system should actively oppose. Today, many of these pro-inflammatory responses can be related to the activation of specific G protein-coupled receptors, including GPR41/FFA3 and GPR43/FFA2 for SCFA; GPR40/FFA1 and GPR120/FFA4 for LCFA, GPR109A/HCA2 for ketone body β-hydroxybutyrate, and GPR81/HCA_1 for lactate, all expressed in different bovine tissues. The activation of these receptors modulates the release of intracellular granules [e.g., metalloproteinase-9 (MMP-9) and lactoferrin], radical oxygen species (ROS) production, chemotaxis, and the production of relevant pro-inflammatory mediators. The article aimed to review the role of natural ligands and receptors and the resulting impact on the host innate immune reaction of cattle and, further, to address the most recent evidence supporting a potential connection to metabolic disorders.

1. Introduction

The bovinea subfamily, which include domestic cattle as well as buffalo species, are raised under intensive management systems to maximize milk and meat production worldwide. Improvements in genetic selection and higher nutritional requirements in bovids are factors associated with a higher incidence of several pathologies, including endometritis (LeBlanc, 2012), mastitis (Gomes et al., 2016), acute aseptic lameness (Thoefner et al., 2005) and polysynovitis (Danscher et al., 2010). These diseases have been associated with the metabolic imbalance of a myriad of compounds in the past, including fatty acids and hydroxycarboxylic acids. Metabolic dysfunction is strongly linked to the host innate immune response involving leukocyte and endothelial cell activation in different mammals, including humans. In cattle, several metabolic disorders are associated with acute inflammatory processes, with polymorphonuclear neutrophils (PMN) being one of the main targets, thereby reducing the first line of defense against invasive pathogens. Activated PMN are known to migrate toward a gradient of chemical messengers [i.e., chemoattractants, such as C-X-C motif chemokine ligand 8 (CXCL8)] at sites of infection and sterile inflammation, produced by other host cells and microorganisms (Wang et al., 2009a). Activated PMN might results in pathogen killing (e.g. bacteria, viruses, fungi, parasites) through three different effector mechanisms: production of reactive oxygen species (ROS), phagocytosis/degranulation and neutrophil extracellular traps (NETs) formation (Kolaczkowska and Kubes, 2013). However, excessive PMN activation, especially surrounding healthy tissues, is known to be harmful to the host and may lead to inflammatory processes, even in the absence

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Table 1
Summary of the main effects from fatty and hydroxycarboxylic acid ligands on different targets in dairy cow.

Receptor	Agonists	Reported expression of the receptor on tissues, cells/cell line of bovines.	Biological Function Suggested	References
FFA1/GPR40	**Natural:** saturated and unsaturated long-chain fatty acids; linoleic acid, oleic acid, palmitic acid **Synthetic:** GW9508, TAK-875, AMG-837, AM-5262, TUG-424, TUG-770, MR1704, CNX-011-67	Cloned bovine mammary epithelial cells (bMEC). Mammary gland Muscle Adipose tissue Neutrophils Bovine umbilical vein endothelial cells (BUVEC) Hepatocytes	-Proliferation and survival of bMEC, through of the activation of the signaling pathways ERK1/2, and Akt -ROS production and MMP-9 activity in bovine neutrophils -Production of pro-inflammatory cytokines in bovine neutrophils through of activation of ERK 1/2, p-38 MAPK pathway and NFκB activation. -Increase of the expression of IL-8 and ICAM-1 and mobilization of intracellular Ca^{+2}	Yonezawa et al. (2008) Friedrichs et al. (2014) Friedrichs et al. (2016) Manosalva et al. (2015) Mena et al. (2016) Loaiza et al. (2016) Aguinaga Casanas et al. (2017)
FFA2/GPR43	**Natural:** short-chain fatty acids (C2-C6); acetate, propionate, butyrate **Synthetic**: 4-CMTB, Phenylacetamide 1, Phenylacetamide 2	Cloned bovine mammary epithelial cells (bMEC). Mammary gland Neutrophils Liver, heart, spleen, skeletal muscle, kidney, cerebral cortex, hypothalamus, pituitary, adrenal gland, lung, pancreas, small intestine (duodenum), colon, rumen, omasum, and reticulum Ruminal epithelium Adipose tissue	Increase of mobilization of intracellular Ca^{+2} in bMEC -Increase of mobilization of intracellular Ca^{+2}, release of MPO, lactoferrin and MMP-9 in bovine neutrophils	Yonezawa et al. (2008) Wang et al. (2009a) Wang et al. (2012) Carretta et al. (2013) Friedrichs et al. (2014) Hosseini et al. (2012), Friedrichs et al. (2016) Lee et al. (2008)
FFA3/GPR41	**Natural:** short-chain fatty acids (C3-C7); acetate, propionate, butyrate **Synthetic:** AR420626	Mammary gland epithelial cells Spleen, Intestine Neutrophils Adipose tissue Hepatocytes	Non-determined	Yonezawa et al. (2008) Wang et al. (2009a) Friedrichs et al. (2014) Friedrichs et al. (2016)
FFA4/GPR120	**Natural:** unsaturated long-chain fatty acids; α-Linolenic acid, docosahexaenoic acid, eicosapentaenoic acid **Synthetic:** GW9508, TUG-891, Compound A, NCG21	Adipose tissue	Non-determined	Agrawal et al. (2017)
GPR84	**Natura**l: medium chain fatty acid; capric acid, decanoic acid, undecanoic acid **Synthetic:** DIM, 6-OAU	Adipose tissue, liver, polymorphonuclear leukocytes (PMNL)	Non-determined	Agrawal et al. (2017)
HCA_2/GPR109A	**Natural:** nicotinic acid, β-hydroxybutyrate **Synthetic:** MK1903	Liver, adipose tissue, muscle, and brain		Titgemeyer et al. (2011), Agrawal et al. (2017)
HCA_1/GPR81	**Natural:** Lactic acid **Synthetic:** Compound 2, 3,5-Dihydroxy-benzoic acid	Adipose tissue	Lipolytic regulation	Sakurai et al. (2014) Feingold et al. (2011) Mielenz (2017)