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Review

Metabolism meets immunity: The role of free fatty acid receptors in the immune system

Elisa Alvarez-Curto *, Graeme Milligan *

Molecular Pharmacology Group, Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, Scotland, United Kingdom

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ABSTRACT

There are significant numbers of nutrient sensing G protein-coupled receptors (GPCRs) that can be found in cells of the immune system and in tissues that are involved in metabolic function, such as the pancreas or the intestinal epithelium. The family of free fatty acid receptors (FFAR1-4, GPR84), plus a few other metabolite sensing receptors (GPR109A, GPR91, GPR35) have been for this reason the focus of studies linking the effects of nutrients with immunological responses. A number of the beneficial anti-inflammatory effects credited to dietary fats such as omega-3 fatty acids are attributed to their actions on FFAR4.This might play an important protective role in the development of obesity, insulin resistance or asthma. The role of the short-chain fatty acids resulting from fermentation of fibre by the intestinal microbiota in regulating acute inflammatory responses is also discussed. Finally we assess the therapeutic potential of this family of receptors to treat pathologies where inflammation is a major factor such as type 2 diabetes, whether by the use of novel synthetic molecules or by the modulation of the individual's diet.

Contents

* Correspondence to: E. Alvarez-Curto or G. Milligan, Molecular Pharmacology Group, Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, Scotland, United Kingdom.
E-mail addresses: Elisa.Alvarez-Curto@glasgow.ac.uk (E. Alvarez-Curto), Graeme.Milligan@glasgow.ac.uk (G. Milligan).

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1. Introduction

The replacement of a regular intake of healthy oils and fibres for a diet based substantially on high fat- and high sugar-content foods has had profound consequences for public health. These changes in the way that the populations of high income, particularly Western countries, manage their dietary habits have undoubtedly triggered what is now considered an epidemic of obesity that has consequently resulted in an increase in serious, chronic conditions associated with dysfunctions of energy balance, including type 2 diabetes and cardiovascular diseases [1,2]. Furthermore, it is now widely accepted that low grade chronic inflammation associated with obesity may be directly connected to other inflammatory related pathologies such as asthma, colitis and, potentially, some forms of cancer, including colon cancer [3–9].

These effects have triggered a major increase in interest with regard to the role of metabolite sensing and how this may affect physiology in health and disease, with concepts including the interface between the metabolic and immune systems, i.e. immuno-metabolism, coming to the front of scientific discussions [9,10]. There has been particular interest in free fatty acid (FFA) sensing and its association with the mode of signalling of a number of recently de-orphanised G protein-coupled receptors (GPCRs) [11]. This is a fast moving and exciting area of research focusing the interest of pharmacologists, chemists, immunologists and physiologists in an interdisciplinary manner. FFAs, including health boosting omega-3 fatty acid containing oils, are therefore no longer considered only as metabolic intermediaries but also as critical signalling molecules due to their role as agonists for different members of the family of free fatty acid receptors (FFARs) [12–16]. Although widely expressed, their presence on key cell types regulating both metabolic and immune health acts to link the regulation of energy homoeostasis with the control of inflammatory responses [17,18].

FFARs are therefore now considered very attractive targets for the development of either novel medicines or novel strategies to treat both metabolic and inflammatory pathologies. However, as they are a relatively newly described group of receptors there remain a substantial number of open questions with regard to their function and the roles that they subserve. This review maps out the key players and connections between FFAs that are obtained through the diet or as a result of the actions of the gut commensal microbiota and the immune system and addresses how further understanding of these systems might be used to limit or treat disease.

2. Overview of the family of free fatty acid receptors

2.1. Free fatty acids

The basic structure of a 'free' fatty acid, i.e. one unbound or non-esterified within larger species such as triglycerides or phospholipids, is a carboxylic acid linked to an aliphatic chain of variable length that may be saturated or unsaturated. As such, fatty acids are widely classified based on the length of their carbon chains and grouped into short chain fatty acids (SCFAs, C2–C6), medium chain fatty acids (MCFAs, C7–C12) and long chain fatty acids (LCFAs, >C12). These may have a number of different origins. Most of the 'essential' fatty acids such as linoleic acid (18:2, n-6) or alpha-linolenic acid (18:3, n-3), which humans cannot synthesise directly, and other LCFAs and MCFAs, are generally obtained through the diet [19,20]. Some other FFAs are obtained through the breakdown of fats (triglycerides) in adipose tissue (AT) and the liver. By contrast the vast majority of SCFAs including acetate (C2) and propionate (C3) are derived from the fermentation of fibres and breakdown of dietary carbohydrates by the bacteria present in the gut [21,22]. As will be discussed further, there is mounting evidence to support a central role for the gut microbiota in the regulation of energy homoeostasis and its impact in inflammatory processes [23–25].

2.2. Free fatty acid receptors

FFARs are members of the 'rhodopsin-like' GPCR family and currently four receptors (FFAR1-4) are so classified. FFAR1, 2 and 3 are closely related in terms of sequence and are co-located (on chromosome 19q13.12 in humans) [26]. Between the coding regions for FFAR3 and FFAR1 (formerly GPR41 and GPR40 respectively) in this chromosome there is a further sequence which was considered initially as a likely pseudogene [27]. However in recent times, analysis of this allele, which is designated as GPR42, has indicated that it may be active in many individuals [28]. It has clearly arisen from a tandem duplication of the *FFAR3* gene as the sequence differs in only 6 amino acids. FFAR2 (formerly GPR43) appears as the last FFAR in the group at this genomic location. In contrast to this group of tandemly encoded sequences, FFAR4 (formerly GPR120) is located on chromosome 10 (10q23.33) in humans and displays little overall homology with the other FFARs. Nevertheless, it was identified as a receptor for LCFAs in 2005 [29]. Previous high-throughput screening and more focussed programmes had led to the de-orphanisation of FFAR1-3 [27,30–33] and these showed that FFAR2 and FFAR3 respond to SCFAs of carbon chain length C2–C6, displaying various potencies for the different ligands [27,33]. In contrast both FFAR1 and FFAR4 are activated selectively by LCFAs. Potentially of importance, although yet to be fully explored, human FFAR4 is produced as two isoforms which differ structurally by a 16 amino acid insertion into the third intracellular loop of the long isoform [34,35]. This is not present in other species investigated to date and although these two isoforms differ in their downstream signal transduction (see Section 2.3 and Table 1) the importance of this for overall function remains unclear, not least because the long isoform has only been detected in a limited number of tissues [35,36].

Although now widely accepted, there was initially debate as to whether the low potencies observed for most FFAs at their receptors, for example propionate displays high microM to low milliM potency at FFAR2 and FFAR3, could be reconciled with them being the true endogenous ligands for the receptors [37]. However, levels of SCFAs in the gut or plasma can reach high milliM levels [31,38–41]. Moreover, LCFAs, although generally displaying low microM potency in *in vitro* assays at FFAR1 and FFAR4, are highly plasma protein bound, e.g. to serum albumin, and it remains uncertain how this affects presentation of the ligands to the relevant receptors *in vivo* or what are the true available ligand amounts.

The modest potency that most FFAs display at their target receptors, and the small chemical size of the SCFAs, has resulted in a view, although atomic level structures of these receptors are not yet available, that the ligand pocket of FFAR2 and FFAR3 must also be small [42]. This has resulted in challenges in terms of the development of novel selective and potent synthetic ligands at these receptors [43]. However, the FFAR2 antagonist GLPG0974 did enter first-in-man clinical trials, even if these were rapidly abandoned, as a potential treatment for the lower gut inflammatory condition ulcerative colitis [44] (see Section 3.1.1 for further details). By contrast, in part because of the clear potential for regulation of glucose homoeostasis and, therefore diabetes, by targeting the receptors for LCFAs, the development of ligands for these receptors is significantly more advanced [44]. For example, the FFAR1 receptor agonist TAK-875/fasiglifam progressed into phase III clinical trials and was able to reduce blood glucose levels, increase insulin levels, and to cause a significant 1.2–1.4%

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