British Journal of Nutrition (2014), **111**, S3–S7
doi:10.1017/S0007114513002249

G-protein-coupled receptors for free fatty acids: nutritional and therapeutic targets

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(Submitted 5 October 2012 – Final revision received 10 December 2012 – Accepted 19 December 2012)

Abstract

It is becoming evident that nutrients and metabolic intermediates derived from such nutrients regulate cellular function by activating a number of cell-surface G-protein coupled receptors (GPCRs). Until now, members of the GPCR family have largely been considered as the molecular targets that communicate cellular signals initiated by hormones and neurotransmitters. Recently, based on tissue expression patterns of these receptors and the concept that they may elicit the production of a range of appetite- and hunger-regulating peptides, such nutrient sensing GPCRs are attracting considerable attention due to their potential to modulate satiety, improve glucose homeostasis and supress the production of various pro-inflammatory mediators. Despite the developing interests in these nutrients sensing GPCR both as sensors of nutritional status, and targets for limiting the development of metabolic diseases, major challenges remain to exploit their potential for therapeutic purposes. Mostly, this is due to limited characterisation and validation of these receptors because of paucity of selective and high-potency/affinity pharmacological agents to define the detailed function and regulation of these receptors. However, ongoing clinical trials of agonists of free fatty acid receptor 1 suggest that this receptor and other receptors for free fatty acids may provide a successful strategy for controlling hyperglycaemia and providing novel approaches to treat diabetes. Receptors responsive to free fatty acid have been of particular interest, and some aspects of these are considered herein.

Key words: G protein-coupled receptors: Free fatty acid: Diabetes: Gut microbiota

G protein-coupled receptors (GPCRs), sometimes also called 7-transmembrane domain receptors, are the largest family of cell-surface, signal-transducing polypeptides. As the molecular targets for a vast range of water-soluble hormones and neurotransmitters, they regulate the physiology and function of essentially all cells and tissues. Because of this, they have also been, by far, the most effectively targeted group of proteins for small-molecule therapeutic medicines designed to modulate or mask pathophysiological manifestations of diseases. Because of the high affinity of many peptides and other hormones for their GPCRs, initial reports of the ability of members of this family to be activated by relatively high concentrations of various nutrients and metabolic intermediates were inferred to have limited physiological relevance. Despite this, it is now widely accepted that molecules including lactate, succinate and free fatty acids are the physiological regulators of specific GPCRs and that as nutritional sensors these receptors can also be targeted therapeutically in areas including metabolic diseases.

Receptors for free fatty acids, FFA1–3

A group of three GPCRs three of which are encoded by the genes of which are closely linked on chromosome 19 in man, respond to free fatty acids of varying chain lengths.

FFA1

FFA1 (previously designated as GPR40)[1] is activated by both saturated and unsaturated medium-chain (carbon chain length 8–12) and longer-chain (carbon chain length 14–22) fatty acids. The activation of this receptor, which is expressed by β-cells of the pancreas as well as other tissues, including enteroendocrine cells of the gut[2], results in enhanced glucose-dependent secretion of insulin[1]. The contribution of enteroendocrine cells to the function of FFA1 is likely to be substantial as each of the L[3], I[4] and K[5] cells has been reported to express this receptor. Based on such studies, a number of preclinical and clinical development programmes are exploring the therapeutic potential of agonists of this

Abbreviation: GPCR, G protein-coupled receptors.

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receptor. The most advanced programme has been carried out for the synthetic ligand TAK-875 ([(3*S*)-6-({2′,6′-dimethyl-4′-[3-(methylsulphonyl)propoxy]biphe-nyl-3-yl}meth-oxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid hemi-hydrate) (Fig. 1)[6,7], which has shown a capacity to reduce the levels of HbA(1c), a marker of improved glycaemic control, in diabetics without a propensity to promote hypoglycaemic episodes as it (similar to other FFA1 agonists) only stimulates insulin secretion in a glucose-dependent manner. Moreover, at least in humans, TAK-875 does not significantly alter the secretion of glucagon[8]. These studies have attracted useful commentaries and generally positive analyses[9,10], although questions remain in terms of the sustainability of effects during long-term treatment. Interestingly, although both the clinical candidate FFA1 agonists TAK-875 and AMG-837 ((*S*)-3-(4-((4′-(trifluoromethyl)biphenyl-3-yl)methoxy)phenyl)hex-4-ynoic acid) (Fig. 1), similar to the free fatty acids, have carboxylate functions that are anticipated to interact with the same pair of arginine residues in FFA1 that have been shown to be integral for the binding and function of the endogenous ligands[11,12], the situation appears to be more complex now. Recently, Lin *et al.*[13] have shown convincingly that not all FFA1 agonist ligands are equivalent in this regard and some may bind in a different manner to the free fatty acids. Furthermore, different synthetic FFA1 agonists also vary markedly in efficacy (a measure of the maximal effect that they are able to produce). Given this information, it is possible that a difference in clinical effectiveness may be observed between different ligands, although it is currently impossible to predict *a priori* if a full agonist of FFA1 or a ligand that binds in a distinct, allosteric manner might offer advantages over a partial agonist such as AMG-837.

FFA2 and FFA3

Although also acting as receptors for free fatty acids, both FFA2 (previously designated as GPR43) and FFA3 (previously designated as GPR41)[1] selectively bind to and are activated by the short chain fatty acids (SCFAs) (carbon chain length 1–6), particularly acetate (C2), propionate (C3) and butyrate (C4). These SCFAs also fulfil much of the nutritional requirements of colonocytes. The SCFAs are generated predominantly in the gut by microbial fermentation of non-digestible carbohydrates. Importantly, from a nutritional perspective, different non-digestible carbohydrates are fermented to produce significantly different levels of C2, C3 and C4. The capacity of the intestinal microflora to generate C3, for example, is defined by the proportions and contributions of different bacterial groups and species as these utilise at least three distinct metabolic pathways to produce C3 as an end product. As alterations in the makeup and extent of the microbiota are associated with inflammation and gut health state[14–16], there is considerable interest in both prebiotic and probiotic strategies to modulate the population and hence the effectiveness of SCFA production[14–16]. As well as being expressed in the distal ileum and colon, close to the site of SCFA production, FFA2 is well expressed by a range of immune cells, including peripheral blood leucocytes, neutrophils and eosinophils, as well as by adipocytes[1]. This expression pattern has also promoted interest in targeting FFA2 as a means to modulate adiposity and to restrict the development of chronic metabolic diseases by limiting sustained, low-grade inflammation. Moreover, the antagonism of this receptor has been suggested as a means to limit the infiltration of neutrophils into the gut and hence counter inflammatory gut conditions such as Crohn's disease and ulcerative colitis. Despite this, mouse FFA2 'knockout' models have provided contradictory evidence as to the likely effectiveness of this approach[17,18], and further analysis is clearly warranted and required. Although clinical development of FFA2-selective ligands is currently at a very early stage, a number of patents describing both FFA2-selective agonists and FFA2-selective antagonists have appeared[19,20] and preliminary data on the effects of FFA2 agonists on the promotion of neutrophil chemotaxis[21] and regulation of glucose uptake in adipocytes[19] have been reported. Moreover, the SCFA-mediated release of glucagon-like peptide 1 from enteroendocrine cells appears to be mediated via FFA2[22].

Although also activated by the same group of SCFAs as FFA2 and with a broadly similar expression profile, FFA3 is less well characterised than FFA2. Despite early work[23] suggesting that it may provide a means to regulate leptin release, this receptor does not appear to be attracting the same level of interest as a therapeutic target as FFA2. To date, there have been no reports of highly selective synthetic ligands of FFA3 that target the same binding site as the SCFAs and, as such, understanding of the detailed function of this receptor lags behind. Despite this, the noted selectivity of a number of small carboxylic acids for either FFA2 or FFA3[24] indicates that, as for FFA2, it should be possible to identify selective, high-potency/affinity ligands for FFA3. Interestingly, the markedly higher potency of C2 to activate human FFA2 *v.* FFA3, which has resulted in the use of acetate as a selective activator of FFA2[22,25], is not preserved in the rat and mouse orthologues[26] (Fig. 2). These observations reflect differences in the extent of ligand-independent constitutive activity[26] and

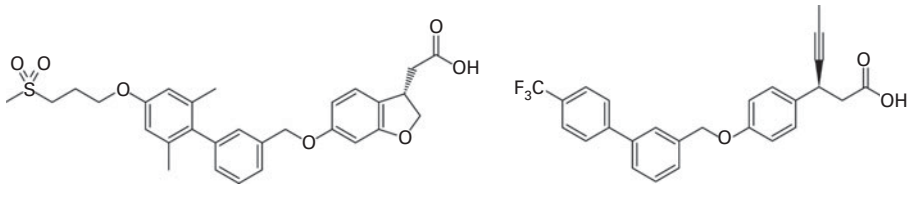

Fig. 1. Structures of FFA1 receptor agonist ligands currently undergoing clinical trials. (a) TAK-875 ([(3*S*)-6-({2′,6′-dimethyl-4′-[3-(methylsulphonyl)propoxy]biphe-nyl-3-yl}meth-oxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid hemi-hydrate) and (b) AMG-837 ((*S*)-3-(4-((4′-(trifluoromethyl)biphenyl-3-yl)methoxy)phenyl)hex-4-ynoic acid).

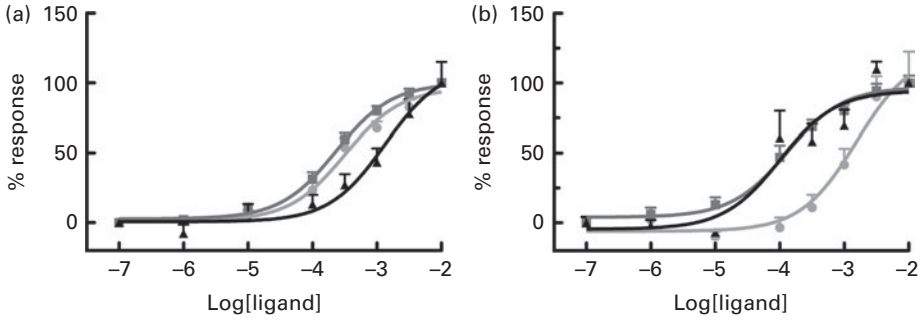

Fig. 2. Differing potencies of SCFAs at human FFA2 and FFA3. The responses to C2 (acetate, ●), C3 (propionate, ■) and C4 (butyrate, ▲) at FFA2 (a) or FFA3 (b) are plotted as the percentage of maximal ligand response as measured in HEK-293 cells using an extracellular signal-regulated kinase 1/2 phosphorylation assay. At FFA2, C2 and C3 are equipotent, while C4 displays lower potency. In contrast, C3 and C4 have similar potency at FFA3, while lower potency is observed for C2.

clearly demonstrate that C2 cannot be used in the absence of 'knockout' or 'knockdown' approaches to implicate a specific role for FFA2 in rodent-derived cell lines and tissues. Additional questions related to how species orthologue variation might affect the function of SCFA receptors arose with the observation that the relative activity of various SCFAs are entirely different at bovine FFA2 than either human or rodent orthologues of FFA2[27]. In particular, the substantially lower potency of C2 as an agonist for bovine FFA2 may reflect underlying physiological differences, with high levels of C2 and the other SCFAs being produced in the rumen and marked expression of the receptor detected in the rumen[28]. Together, these observations suggest significant species orthologue variation in the pharmacology of the SCFA receptors with regard to their endogenous ligands, which probably will translate to some degree of species selectivity in the pharmacology of synthetic ligands targeting these receptors. This, in turn, may hinder further validation of these receptors as therapeutic targets.

Other G protein-coupled receptors activated by free fatty acid

GPR84

Although recognised as a receptor responsive to medium-chain saturated free fatty acid[29], GPR84 remains, by far, the least studied and understood of the currently described receptors for free fatty acid. Expressed predominantly by various immune cells[29], interest in GPR84 has recently increased due to studies in which co-culture of model macrophages and adipocytes has been found to result in marked up-regulation of GPR84 expression by the adipocytes[30]. As there is considerable interest in the contribution of infiltrating macrophages to adipose tissue function, such regulation of GPR84 might be a target to limit the effects of increased fat mass and adiposity in metabolic and other co-morbid diseases, but detailed assessment of this will not be possible without the development of useful pharmacological regulators for this receptor.

GPR120

A second receptor activated by medium-chain and long-chain free fatty acids is GPR120. GPR120 is sometimes described as a receptor for the *n*-3 group of PUFAs[31,32] that are present in good amounts in oily fish[33] and have clear health benefits in areas ranging from cardiovascular function to inflammation. However, it is clear that such PUFAs have a wide range of other molecular targets, including FFA1, and that other, less-health-beneficial fatty acids can also activate this receptor. Despite these issues, a number of observations have suggested that the activation of GPR120 could have therapeutic benefits. Key among these are reports that GPR120 may have a specific capacity to mediate the action of long-chain fatty acids in promoting the secretion of the incretin glucagon-like peptide 1 from enteroendocrine cells of the gut[34] and indications that the activation of GPR120 produces extensive anti-inflammatory and resulting insulin-sensitising effects[31]. Specifically, the activation of GPR120 has been reported to suppress the release of pro-inflammatory cytokines from macrophages, which, given the importance of inflammation in obesity-related insulin resistance, has led to the speculation that the activation of GPR120 may therapeutically improve insulin resistance[34]. Although potentially of great importance, the studies demonstrating these effects of GPR120 activation have been based on the use of non-selective or poorly selective fatty acids or synthetic ligands as agonists. Hence, although supported in part by mRNA knockdown and/or knockout studies, these require replication using highly selective pharmacological ligands before GPR120 can be truly validated as a viable therapeutic target. Furthermore, the pattern of expression of GPR120 in enteroendocrine cells appears to be similar to that of FFA1 with at least L[3] and K[5] cells being shown to co-express the two receptors. This further highlights the need for highly selective ligands to probe the function of GPR120. Although a number of patents[35,36] describing GPR120-selective ligands have been described, only recently has a series of potent and specific ligands for GPR120 been described in the primary literature[37]. Hopefully, these and other ligands will now allow such ideas to be re-examined.

A recent pair of publications has provided further physiological and potential genetic support to favour agonism of GPR120 as a potential therapy in diabetes. In the studies carried out by Taneera *et al.*[38], the GPR120 receptor gene (*FFAR4*) was identified as a gene strongly associated with diabetes and *FFAR4* mRNA levels were reported to be substantially lower in islets isolated from cadavers of diabetics than

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in those from non-diabetic controls. Moreover, the studies carried out by Ichimura *et al.*[39] identified a non-synonomous SNP (Arg270His) in the open reading frame of human *FFAR4* that was linked to obesity in a European population. *In vitro* assays have indicated that this polymorphism results in virtual abolition of receptor-mediated elevation of intracellular Ca^{2+} levels[39]. However, a number of caveats must be noted about these studies. Humans are apparently the only higher species in which an additional, longer, isoform of the GPR120 receptor has been described alongside the short isoform that is found in both humans and other species[40]. Moreover, careful *in vitro* studies have shown the major allele of the long isoform to be unable to mediate the elevation of Ca^{2+} levels[41]. As the Arg270His position reported for the polymorphic variant indicates that it must have been the long isoform that was employed in these studies (the polymorphism would correspond to Arg254His in the shorter isoform), it is unclear as to how the minor allele SNP could result in the ablation of a function that is reportedly already lacking for the major allele. This discrepancy may simply reflect a sequence position reporting error, but clearly requires further and additional verification. Despite such concerns, the current body of evidence suggests many positive and mutually reinforcing reasons to promote GPR120 as a promising therapeutic target. The potential capacity to regulate glucagon-like peptide 1 secretion in the gut, to promote insulin release, probably via paracrine effects, from the pancreas and to constrain adiposity and reduce insulin resistance via anti-inflammatory mechanisms is favourable. Although recent efforts in medicinal chemistry have been focused on improving the selectivity of ligands between FFA1 and GPR120[37], there is also a strong argument to be made that combined FFA1/GPR120 agonists might display greater anti-diabetic efficacy than targeting either receptor selectively. This, however, remains to be tested.

Conclusions

GPCR responsive to longer-chain free fatty acid function as nutrient sensors for this important group of ligands. Because of this, they are being explored as therapeutic targets to regulate metabolic diseases. Furthermore, growing recognition of the ability of the gut microbiota to influence health via the production of SCFAs as a consequence of the fermentation of non-digestible carbohydrate has led to further attention being paid to the association between nutrition and the development of long-term chronic disorders that are among the most urgent to target therapeutically. Such appreciation is rapidly resulting in a new focus on the interrelationship between nutrients, the microbiota and long-term human health.

Acknowledgements

The present work was supported by Strategic Partnership on Food & Drink Science, Scottish Government Programme of Research 2011-6/Ref UGW 854/11 (to G. M.), Wellcome Trust 089600/Z/09/Z (to G. M.), the Danish Council for Strategic Research 11-116196 (to T. U. and G. M.) and the Canadian Institutes of Health Research (fellowship to B. D. H.).

The authors' contributions are as follows: G. M. and B. D. H. coordinated the writing of the paper with substantial input from both T. U. and H. M. and B. D. H. generated the figures.

The authors declare no conflicts of interest

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