

Endogenous metabolites as ligands for G protein-coupled receptors modulating risk factors for metabolic and cardiovascular disease

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Tonack S, Tang C, Offermanns S. Endogenous metabolites as ligands for G protein-coupled receptors modulating risk factors for metabolic and cardiovascular disease. *Am J Physiol Heart Circ Physiol* 304: H501–H513, 2013. First published December 15, 2012; doi:10.1152/ajpheart.00641.2012.—During the last decade, several G protein-coupled receptors activated by endogenous metabolites have been described. These receptors respond to fatty acids, mono- and disaccharides, amino acids, or various intermediates and products of metabolism, including ketone bodies, lactate, succinate, or bile acids. Receptors of endogenous metabolites are expressed in taste cells, the gastrointestinal tract, adipose tissue, endocrine glands, immune cells, or the kidney and are therefore in a position to sense food intake in the gastrointestinal tract or to link metabolite levels to the appropriate responses of metabolic organs. Some of the receptors appear to provide a link between metabolic and neuronal or immune functions. Given that many of these metabolic processes are dysregulated under pathological conditions, including diabetes, dyslipidemia, and obesity, receptors of endogenous metabolites have also been recognized as potential drug targets to prevent and/or treat metabolic and cardiovascular diseases. This review describes G protein-coupled receptors activated by endogenous metabolites and summarizes their physiological, pathophysiological, and potential pharmacological roles.

fatty acid; carbohydrates; ketone bodies; lactate; bile acid; G protein-coupled receptors

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Introduction

G protein-coupled receptors (GPCRs) have originally been described as a family of receptors activated by hormones, neurotransmitters, and other mediators. However, during the last decade, an increasing number of GPCRs has been identified, which are activated by ligands primarily known as endogenous metabolites, which serve functions other than as signaling mediators. Most of these endogenous metabolites are substrates or intermediates of energy metabolism, and their plasma concentration often indicates particular metabolic or nutritional states. During evolution, higher organisms have obviously taken advantage of this fact and have developed receptors to use this information to sense, for instance, metabolic activities or nutritional states. Many of these receptors appear to be not only involved in the regulation of metabolic

functions under physiological conditions but can also be involved in dysregulation under pathological conditions.

Metabolic diseases, such as obesity, type 2 diabetes, or dyslipidemia, are an increasing problem worldwide with dramatic consequences, as they also predispose to other diseases, such as cardiovascular disorders or cancer (38, 82). Lifestyle and genetic predisposition are the major factors causing metabolic disorders (6, 46, 119), but many of the mechanisms underlying the development and progression of metabolic diseases are still unclear. A better understanding of the regulatory mechanisms controlling metabolic functions in health and disease is required to develop novel pharmacological strategies to prevent or treat these disorders. As GPCRs are ideal drug targets, it is obvious that receptors for endogenous metabolites bear considerable potential as targets for new therapeutic strategies. For most of these receptors, synthetic ligands have been developed, and, in some cases, promising clinical studies have been initiated to test the potential of these ligands in the prevention or treatment of metabolic disorders.

In this review, we will summarize current knowledge on GPCRs activated by endogenous metabolites and discuss their function in the cardiovascular and metabolic system.

Lipids

Dietary triglycerides are important nutrients and energy sources. Pancreatic lipase hydrolyzes triglycerides to free fatty acids (FFAs) and 2-monoacylglycerol, which are taken up in the

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intestinal tract (111). Work of recent years has shown that, in particular, long-chain fatty acids are not only essential energy substrates but also function as signaling molecules that can regulate cellular processes in particular cells. Several GPCRs activated by long-chain fatty acids have been identified (Table 1) (52, 145, 181). In addition, there are receptors activated by short-chain fatty acids, such as acetate, propionate, and butyrate, that are produced by anaerobic bacterial fermentation of dietary fibers in the intestine (54, 124, 167, 178).

Long-chain fatty acids. Two GPCRs have been described to be activated by long-chain fatty acids: FFA receptor 1 [FFA₁; also known as GPCR (GPR)40] and GPR120. FFA₁ (or GPR40) is activated by medium- and long-chain fatty acids and is coupled to G_{q/11} (16). FFA₁ is expressed in β -cells of pancreatic islets (64), enteroendocrine cells (37), immune cells (55), taste buds (22), and the central nervous system (102). The expression of FFA₁ in pancreatic α -cells is controversial (41, 55).

Activation of FFA₁ by fatty acids on β -cells stimulates insulin secretion in a concentration-dependent manner (64), and, in addition, Edfalk et al. (37) provided evidence that FFA₁ mediates fatty acid-stimulated insulin secretion indirectly by the activation of enteroendocrine cells and release of incretins, such as glucagon-like peptide (GLP)-1 and gastric inhibitory polypeptide (GIP). Using mice lacking or overexpressing FFA₁ in pancreatic β -cells, Steneberg et al. (166) showed that FFA₁ deficiency protected mice from obesity-induced hyperinsulinemia, hepatic steatosis, and impaired glucose tolerance, whereas chronic FFA₁ overexpression led to impaired β -cell

function, hypoinsulinemia, and overt diabetes. However, a subsequent study (75) came to different conclusions and found that FFA₁-deficient mice have fasting hyperglycemia and are not protected from high-fat diet-induced insulin resistance and liver steatosis. In addition, using transgenic mice overexpressing FFA₁ in pancreatic β -cells under a different promoter, Nagasumi et al. (113) found that chronic activation of FFA₁ augmented glucose-stimulated insulin secretion and resulted in improved glucose tolerance. This research indicated that specific FFA₁ agonists may be useful in the treatment of type 2 diabetes.

Although Hirasawa et al. (55) could barely detect FFA₁ expression in pancreatic α -cells, Flodgren et al. (41) found colocalization of FFA₁ and glucagon in α -cells using a different antibody against FFA₁ and demonstrated that glucagonoma cells as well as isolated mouse pancreatic islets secrete glucagon in response to linoleic acid, an endogenous ligand of FFA₁. This response was likely to be mediated by FFA₁, as it was abolished by treatment of cells with antisense oligonucleotides directed against FFA₁ (41). To what extent this regulation contributes to the overall metabolic effects of long-chain fatty acids mediated by FFA₁ is unclear.

Recently, many selective FFA₁ agonists with high potency and good pharmacokinetic features have been developed. Several of them, including AMG-837 and TAK-875, have been shown to potentiate glucose-stimulated insulin secretion (4, 59, 96). A phase II clinical study with the FFA₁ agonist TAK-875 has recently provided promising data by exhibiting an effica-

Table 1. *G protein-coupled receptors activated by fatty acids and 2-monoacylglycerols*

Ligand(s)	Receptor	Aliases	Other Ligands (Selection)	G Protein(s)	Expression (Major Effects)	References
<i>Fatty acid receptors</i>						
Medium- and long-chain fatty acids, C8–C22	FFA ₁	GPR40, FFAR1	Agonists: AMG-837 and TAK-875	G _q /G ₁₁	β -Cells of the pancreas (increase in GSIS), enteroendocrine cells (increase in GLP-1/GIP secretion), immune cells, taste buds, and central nervous system	4, 16, 22, 37, 55, 59, 64, 96, 102
Long-chain fatty acids, C14–C22	GPR120	PGR4, GPR129, GT01	Agonists: NCG-21, compounds 43, 25, and 15, and ω -3 fatty acids	G _q /G ₁₁	Enteroendocrine cells (increase in GLP-1/GIP secretion), adipocytes, macrophages (decreased in inflammatory signaling), and type II taste cells	44, 56, 109, 110, 125, 161, 169
Medium-chain fatty acids, C9–C14	GPR84	EX33, GPCR4	Agonist: compound 1	G _i	leukocytes, adipose tissue	48, 112, 185
Short-chain fatty acids, C2–C5	FFA ₂	GPR43, FFA2R, FFAR2, GPCR3	Allosteric agonist: compound 58; orthosteric agonist: compound 39; and antagonist: compound 4	G _q /G ₁₁ , G _i	Enteroendocrine cells (increase in GLP-1 secretion), adipocytes, neutrophils (chemotaxis), eosinophils, and pancreatic islets	15, 17, 58, 60, 92, 93, 117, 176, 186
Short-chain fatty acids, C2–C5	FFA ₃	GPR41, FFAR3, FFA3R, GPCR41, LSSIG		G _i	Enteroendocrine cells, pancreatic islets, and sympathetic ganglia (increase in norepinephrine release)	17, 83, 92, 117, 176
<i>2-Monoacylglycerol receptor</i>						
2-Monoacylglycerol	GPR119	GPCR2	Lysophosphatidylcholine, oleylethanolamide, ADP-597, GSK-1292263, and MBX-2982	G _s	Enteroendocrine cells (increase in GLP-1/GIP secretion) and pancreatic β -cells of the pancreas (increase in GSIS)	30, 49, 50, 127, 130, 147, 165

FFA, free fatty acid (type receptors); GPR, G protein-coupled receptor; GSIS, glucose-stimulated insulin release; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide.

cious glucose-lowering activity with a relatively low risk of hypoglycemia (4, 18).

GPR120, which is only distantly related to FFA₁, is also coupled to G_{q/11} and is activated by long-chain fatty acids with a carbon chain length of C14–C22 (56). GPR120 is expressed in enteroendocrine cells (56), adipocytes (44), macrophages (125), and type II taste cells (109, 110).

GPR120 was originally shown to mediate fatty acid-stimulated GLP-1 secretion from enteroendocrine cells; the released GLP-1, in turn, promotes glucose-stimulated insulin secretion from pancreatic β -cells (56). There is also evidence that GPR120 mediates fatty acid-induced secretion of the gut peptide hormone cholecystokinin (CCK) (171). In addition, long-chain fatty acids may stimulate adipogenesis via GPR120 activation (44), a notion supported by a more recent study (61) showing that GPR120 deficiency leads to impaired adipocyte differentiation.

GPR120-deficient mice fed a normal diet develop hyperinsulinemia and mild glucose intolerance due to the development of insulin resistance (125). ω -3 Fatty acids, which are also agonists for GPR120, can improve insulin sensitivity and reduce inflammatory activity in obese mice, and this beneficial effect was abolished in GPR120-deficient mice (125). GPR120-mediated anti-inflammatory and insulin-sensitizing effects may be due to the inhibition of transforming growth factor- β -activated protein kinase (TAK)1-binding protein 1-mediated activation of TAK1, thereby inhibiting a central proinflammatory signaling pathway (123, 125). Together with a recent study (61) showing that loss of function GPR120 gene variants are associated with an increased risk for obesity and insulin resistance in both mice and humans, these data indicate that agonists of GPR120 may be able to improve glucose tolerance and other metabolic functions.

While Oh et al. (125) found that insulin sensitivity was unaltered in GPR120-deficient mice fed a high-fat diet for 20 wk, Ichimura et al. (61) observed impaired insulin sensitivity in GPR120-deficient mice kept on high-fat diet for only 11 wk, accompanied by the development of obesity, glucose intolerance, and fatty liver with decreased adipocyte differentiation as well as enhanced hepatic lipogenesis. The authors (61) also identified a variant of GPR120 (R270H) that lacks the ability to transduce the signal of long-chain fatty acids and appears to be associated with the development of obesity in humans.

Although GPR120 agonism is supposed to have beneficial effects, only a few specific GPR120 agonists are so far available. Based on a newly proposed prediction model, GPR120 agonists with improved selectivity over FFA₁ have been developed, of which NCG21 was shown to activate GPR120 with a pEC₅₀ of 5.9 (169). More recently, the first potent and selective GPR120 agonist, compound 43, has been described, which activates GPR120 with an EC₅₀ in the higher nanomolar range (161).

Medium-chain fatty acids. GPR84 is a receptor for medium-chain fatty acids with a chain length of C9–C14, with C10–C12 being the most potent species. GPR84, which is primarily coupled to G_i (185), is expressed in various leukocytes, including monocytes and neutrophils (185). Recently, GPR84 was also found to be expressed in adipose tissue, and expression of GPR84 in this tissue was enhanced under high-fat diet and inflammatory conditions, suggesting a possible role of GPR84 in modulating the function of adipocytes and immune cells

(112, 185). However, the biological function of this receptor remains to be defined.

Short-chain fatty acids. The short-chain FFA receptors FFA₂ (GPR43) and FFA₃ (GPR41) are encoded by genes located next to each other on the chromosome. They are activated by fatty acids with a chain length of C2–C5 (acetate, propionate, butyrate, and pentanoate). FFA₂ prefers acetate and propionate, whereas FFA₃ prefers propionate and butyrate; both receptors couple to G_i, and FFA₂ also binds to G_{q/11} (17, 92, 117). The expression patterns of FFA₂ and FFA₃ are overlapping in pancreatic islets and enteroendocrine cells, in particular in GLP-1- and peptide YY (PYY)-containing L cells (71, 72, 146, 153, 173, 176). FFA₂ is also expressed in adipocytes of white adipose tissue (58), whereas the expression of FFA₃ in adipose tissue is controversial. In early studies (17, 196) FFA₃ was described to be expressed in mouse and human white adipose tissue, but other groups (58, 83, 146) were not able to confirm this. The expression of FFA₂ is upregulated in adipose tissue of mice fed a high-fat diet (58) and was found to be slightly reduced in mice lacking FFA₃ (199), whereas the expression of FFA₃ in adipose tissue strongly increased in FFA₂-deficient mice (11). The latter finding suggests that FFA₃ could partly compensate for the loss of FFA₂ in adipose tissue. FFA₂ is also expressed in a variety of immune cells, in particular neutrophils (17, 92, 117), whereas FFA₃ is detected in sympathetic ganglion neurons (83).

FFA₃-deficient mice maintained on a standard polysaccharide-rich chow diet showed less adiposity and less PYY secretion from enteroendocrine cells; however, these effects disappeared when mice were kept in germ-free conditions, indicating that short-chain fatty acids derived from the gut microbiota exert receptor-mediated effects on host adiposity (153). Therefore, the authors suggested that antagonists of FFA₃ could lead to decreased extraction of energy from the diet and thus would be potential drugs for the treatment of obesity. However, a recent study (83) has suggested a potential risk of FFA₃ antagonists, as it showed that FFA₃ deficiency could lead to a decrease in heart rate caused by lowered norepinephrine levels. This effect is believed to be due to the ability of FFA₃ to mediate norepinephrine release from sympathetic nerve terminals via a G _{β - γ} -phospholipase C (PLC)- β -MAPK signaling pathway (62, 83). Xiong et al. (196) reported that FFA₃ mediates short-chain fatty acid-induced leptin secretion in adipose tissue, and another group (199) confirmed the stimulatory effect of short-chain fatty acids on leptin secretion but found evidence that this effect is dependent on FFA₂ rather than on FFA₃.

The role of FFA₂ in the regulation of host metabolism is still not clear. In mice lacking FFA₂ fed a high-fat diet, Bjursell et al. (11) described reduced weight gain accompanied by a somewhat improved glucose tolerance and slightly decreased insulin secretion compared with wild-type animals. No differences were reported under a normal chow diet. However, using normal chow diet-fed FFA₂- and FFA₃-deficient mice on a mixed 129/SvEv background, Tolhurst et al. (176) reported a phenotype of glucose intolerance accompanied with diminished insulin secretion in single-knockout mice, which was attributed to impaired GLP-1 secretion from L cells of FFA₂- and FFA₃-deficient mice.

Given that FFA₂ and FFA₃ share, at least partially, the same endogenous ligands and have quite similar expression patterns, their functions may be overlapping, and the results of studies in

single-deficient mice are difficult to interpret. More work is needed to understand the function of these two receptors under *in vivo* conditions.

2-Monoacylglycerol. The receptor GPR119 can be activated by a variety of endogenous and dietary lipid metabolites (49). Among them are 2-monoacylglycerols, oleoylethanolamide, and lysophospholipids, such as lysophosphatidylcholine (50, 127, 165). GPR119 is mainly expressed in β -cells of pancreatic islets as well as in enteroendocrine K and L cells, which produce GIP and GLP-1, respectively (30, 130, 147). Activation of GPR119 on β -cells or enteroendocrine cells results in an increase in cAMP levels, presumably through the activation of G_s (29, 30, 152, 165). In pancreatic β -cells, this results in an increase in glucose-stimulated insulin secretion, whereas GPR119 activation in enteroendocrine cells stimulates the release of the incretin hormones GLP-1 and GIP, which, in turn, promote insulin secretion from pancreatic β -cells (29, 30, 89, 152, 165). Thus, GPR119 can directly and indirectly promote insulin secretion from pancreatic β -cells. Mice lacking GPR119 have a lower body weight, and postprandial levels of GLP-1 were reduced, suggesting that dietary components increase GLP-1 secretion through GPR119 (90). Good candidates for mediating diet-induced GLP-1 release through GPR119 are 2-monoacylglycerols, which can activate GPR119 and are present at sufficient levels in the lumen of the intestine (50). However, whether 2-monoacylglycerols are indeed the relevant endogenous ligands of GPR119 is still unclear. In future work, pharmacological and genetic tools are required to obtain further insights into GPR119 function under physiological and pathophysiological conditions. Given the role of GPR119 in the stimulatory regulation of incretin and insulin secretion, agonists of this receptor have been suggested as potential therapeutics to treat type 2 diabetes, and several synthetic GPR119 agonists have provided promising results in preclinical studies (49, 68, 160).

Carbohydrates

The only GPCR activated by carbohydrates is the dimeric sweet taste type 1 receptor (T1R), T1R2/T1R3, which binds various monosaccharides and polysaccharide carbohydrate sugars, including glucose, fructose, sucrose, maltose, or lactose, when present at millimolar concentrations (95, 115, 201). The sweet receptor is best known for its role as a sensory receptor expressed by distinct cells in the taste buds of the tongue, where it mediates the sensation of sweet taste (24). Specialized sweet-sensing cells in the taste buds express the sweet receptor and couple it through G proteins of the G_i family, in particular gustducin, to the activation of the β_2 -isoform of PLC and the transient receptor potential (TRP) protein TRPM5 (200), which eventually results in the depolarization of sweet-sensing taste cells. However, expression of the mono- and disaccharide receptor T1R2/T1R3 has also been described in other metabolically relevant cells, such as enteroendocrine cells and cells of the pancreatic islets (65, 84, 86). In pancreatic β -cells, T1R2/T1R3 has been suggested to mediate fructose-induced potentiation of postprandial glucose-stimulated insulin secretion (86). The potential role of T1R2/T1R3 in enteroendocrine cells has been controversial. Several groups (65, 85) have found its expression in enteroendocrine cells of various species and could demonstrate that lack of

T1R3 in mice results in a reduced glucose-induced release of GLP-1. Consistent with this, lactisole, a negative allosteric modulator of T1R2/T1R3, attenuates glucose-stimulated secretion of GLP-1 and PYY (42). Others (9, 131, 147) have failed to detect its expression in enteroendocrine cells and have proposed alternative mechanisms mediating glucose-induced GLP-1 secretion from enteroendocrine cells. In addition to enteroendocrine cells, there is also evidence that the receptor is expressed in enterocytes, where it can regulate glucose-induced upregulation of Na^+ -dependent glucose transporter 1 (SLC5A1) (105).

Thus, there is increasing evidence that the sweet receptor T1R2/T1R3 is not only involved in the gustatory function of sweet sensation but may also mediate direct metabolic effects of mono- and disaccharides. However, its exact role remains to be clarified. Given that artificial sweeteners activating or modulating T1R2/T1R3 have been widely used and are currently being further developed (159), it will also be important to explore the potential of beneficial or harmful effects of these synthetic sweet receptor ligands in metabolic regulation.

Amino Acids and Peptone

Several amino acids but also peptone, a mixture of peptides and amino acids derived from protein hydrolysis by pepsin or acids, can activate certain GPCRs. Whereas GPR93 has been reported to be activated by peptone, several receptors belonging to the class C family of GPCRs respond to particular amino acids (Table 2). GPCRs of class C function as homodimers or heterodimers, and their relatively large extracellular domains are characterized by the so-called Venus flytrap motif, which, in many cases, is involved in ligand binding (32, 192).

Peptone. GPR93 has been shown to be present in enterocytes and to be activated by protein hydrolysates (peptone) (26, 27). The receptor is activated by peptone with an EC_{50} of 4 mg/ml and appears to couple to several G protein families (26, 27). Which components of peptone are eventually responsible for GPR93 activation is still unclear. Together with data in CCK-producing cell lines (27), this led to the hypothesis that GPR93 mediates peptone-induced CCK-release from L cells. *In vivo* data supporting a role of GPR93 in mediating peptone-induced CCK release are, however, missing, and more work is required to define the potential role of GPR93 in mediating the effects of peptone.

Amino acids. The heterodimeric taste receptor T1R1/T1R3 is known to respond to glutamate and to mediate the so-called umami taste (95, 114). The murine receptor also senses millimolar concentrations of other L-amino acids, except for aromatic amino acids, whereas the human receptor prefers L-glutamate over other amino acids (24). Activation of T1R1/T1R3 by L-amino acids can be potentiated by inosine 5'-monophosphate and GMP (114). T1R1/T1R3 is coupled to G_i -type G proteins, including gustducin and transducin, and is expressed in taste buds of the tongue (24). Expression has also been described in epithelial cells of the stomach and intestine (9), and Mace et al. (103) described that T1R1/T1R3 is localized in the apical membrane of the rat jejunum. However, other studies (130, 147, 148) have shown very low mRNA levels in the stomach and intestine and no evidence for T1R1 and T1R3 expression in enteroendocrine cells. Further studies are needed to clarify a potential role of T1R1/T1R3 in gut chemosensing.

Table 2. *G protein-coupled receptors activated by carbohydrates, amino acids, and peptones*

Ligand(s)	Receptor	Aliases	Other Ligands (Selection)	G Protein(s)	Expression	References
<i>Carbohydrates</i>						
Glucose, lactose, fructose, maltose, and sucrose	T1R2/T1R3	TAS1R2/TAS1R3	Orthosteric agonist: aspartame; allosteric agonist: cyclamate and S-819; negative allosteric modulator: lactisole; and positive allosteric modulator: SE-2 and SE-3	Gustducin, G _i ?	Type II taste cells, enteroendocrine cells?, and pancreatic islets	65, 84, 86, 95, 115, 200, 201
<i>Peptone</i>						
Peptone	GPR93	GPR93, GPR92, LPAR5, LPA5	Agonist: lysophosphatidic acid, farnesyl monophosphate, and farnesyl diphosphate; and antagonist: AM-966	G _q /G ₁₁ , G _i , G _s , G _{12/13}	Gastrointestinal tract, lung, heart, spleen, thymus, skin, and liver	25, 193
<i>Amino acids</i>						
L-Glutamate and other nonaromatic amino acids (human)	T1R1/T1R3	TAS1R1, GPR70/TAS1R3	Agonist (human): L-AP4; and positive modulators: GMP and inositol 5'-monophosphate	Gustducin, transducin	Taste buds of the tongue and enteroendocrine cells	24, 95, 114
Basic amino acids (glycine, L-alanine, L-serine, and L-cysteine)	GPRC ₆	GPRC6A	Agonist: testosterone and osteocalcin; and positive modulator: Ca ²⁺	G _q , G _i , G _s ?	Widely, including the lung, liver, spleen, heart, kidney, skeletal muscle, testis, brain, bone, gastric mucosa, and pancreatic β-cells	39, 134-136, 163, 191, 192
Aromatic amino acids and other amino acids (positive allosteric modulators)	CaSR	CaS, CaR, Gprc2a	Agonists: Ca ²⁺ , spermine, and neomycin; antagonists: NPS-2143, CMP-2H, and calhex 231; and positive allosteric modulators: cinacalcet and calindol	G _{q/11} , G _{i/o} , G _{12/13}	Widely, including the chief cells of the parathyroid gland, kidney, chondrocytes, cardiomyocytes, adipocytes, pancreatic β-cells, enteroendocrine cells, central nervous system, and keratinocytes	23, 33, 34, 47, 81, 97, 116, 143, 149, 168, 188

T1R, taste type 1 receptor; CaSR, Ca²⁺-sensing receptor.

GPRC6A is a receptor for L-amino acids, in particular basic amino acids (190, 191), and its activation by amino acids can be potentiated by divalent cations (28). The receptor is also activated by osteocalcin and testosterone (126, 135, 136, 138). GPRC6A signals via G_q and G_i, and there is also evidence for cell type-specific coupling to G_s (136). The receptor is widely expressed in the body (190) and might be involved in the regulation of metabolic processes. Two different mouse models lacking GPRC6A have been developed (134, 192). Whereas mice in which exon 2 of the GPRC6A gene was deleted have been reported to exhibit a complex metabolic phenotype including hyperglycemia, glucose intolerance, and insulin resistance as well as impaired bone mineral density, defective testicular function, proteinuria, and renal calcium and phosphate wasting (134), none of these defects were reported in mice lacking exon 6 of the GPRC6A gene (192). Similar differences were reported regarding a potential role of GPRC6A in the regulation of insulin secretion. Whereas Pi et al. (137, 138) found evidence that GPRC6A mediates osteocalcin- and L-arginine-induced insulin secretion from β-cells, Smajilovic et al. (163) detected GPRC6A expression in pancreatic islets but found no evidence for a role in the mediation of L-arginine-induced insulin secretion. These differences may

be due to the different genetic mouse models and/or experimental conditions (163). GPRC6A was found expressed in the antral gastric mucosa colocalized with gastrin and somatostatin, suggesting a role of GPRC6A in amino acid sensing in the stomach (47). However, functional data supporting this are missing.

The Ca²⁺-sensing receptor (CaSR), closely related to GPRC6A, is widely expressed and was first described as a receptor sensing extracellular calcium ions and regulating calcium homeostasis (174). Mice lacking the receptor showed that CaSR plays a key role in parathyroid and kidney Ca²⁺ sensing (57). CaSR can also bind L-amino acids, which results in an allosteric enhancement of its sensitivity to extracellular calcium (33). In contrast to GPRC6A, CaSR preferentially binds aromatic amino acids (34). CaSR is primarily coupled to G_q but has also been reported to be able to activate other G protein families (187). The receptor is expressed by various cells of the gut epithelium, including gastrin-producing G cells, somatostatin-producing D cells (47), and CCK-producing I cells (97). In these cell types, the receptor may mediate the amino acid-induced secretion of intestinal hormones. In primary I cells from mice lacking CaSR, CCK release induced by L-phenylalanine was significantly reduced (97). There is also evidence

that the receptor mediates L-amino acid-stimulated gastric acid secretion in parietal cells (19).

Apart from its role in enteroendocrine cells, several other metabolic functions appear to be regulated through CaSR. There is good evidence that the receptor is expressed by pancreatic β -cells and can promote glucose-induced insulin secretion (45, 129, 155). In addition, CaSR can mediate inhibition of lipolysis in adipocytes (31). The receptor may be involved in the induction of cardiomyocyte apoptosis under ischemic conditions (197, 202) but has also been reported to mediate the cardioprotective effects of preconditioning (168).

The amino acid glutamate is an important neurotransmitter that acts through ionotropic and metabotropic receptors. The metabotropic glutamate receptors are a group of eight GPCRs belonging to family C of GPCRs, which are best known for their important role in modulating synaptic transmission and neuronal excitability in the central nervous system (118). The potential role of metabotropic glutamate receptors in mediating effects outside the nervous system and their potential role in responding to nutritional glutamate have been poorly described, although metabotropic glutamate receptors have been found in a variety of non-neural tissues (69).

Metabolic Intermediates

Several end products or intermediates of anaerobic glycolysis, β -oxidation, the tricarboxylic acid cycle, ketogenesis, or cholesterol metabolization have been shown to specifically activate GPCRs, and the key role that these metabolic intermediates play in metabolic regulation suggests that these re-

ceptors respond to particular metabolic situations to allow adaptation to them. Among these receptors are the hydroxycarboxylic acid (HCA) receptors, which are activated by lactate, the ketone body 3-hydroxybutyrate, the β -oxidation intermediate 3-hydroxyoctanoate (2, 122), and receptors for the tricarboxylic acid cycle intermediate succinate (5) or for bile acids (140) (Table 3).

Lactate. Lactate at low millimolar concentrations activates the HCA type 1 receptor (HCA₁; also known as GPR81) (20, 99). This receptor is coupled to G_i-type G proteins and is primarily expressed in white adipocytes (3, 20, 40, 67, 99). Activation of the receptor results in an antilipolytic effect (3, 40, 67, 98). Experiments in mice lacking HCA₁ have indicated that the receptor is involved in the anabolic effects of insulin in adipocytes. After insulin-mediated glucose uptake, local lactate levels in adipose tissue increase severalfold due to the conversion of glucose to lactate by adipocytes (3, 36, 66, 144). Lactate then acts in an auto-/paracrine manner to inhibit cAMP production via HCA₁ and thereby induces an inhibition of lipolysis (3). Thus, insulin inhibits lipolysis through a phosphodiesterase 3B-mediated increase in cAMP degradation as well as by a lactate/GPR81-mediated decrease in cAMP production (3, 87). Besides the role of HCA₁ in the short-term regulation of adipocyte function, the receptor also appears to be involved in the long-term regulation of energy storage as HCA₁-deficient mice gained less weight compared with wild-type animals when fed a high-fat diet (3). This suggests that the lack of HCA₁-mediated insulin-induced anabolic effects in the long run results in a reduced storage of energy in adipose

Table 3. G protein-coupled receptors activated by various metabolic intermediates

Metabolic Intermediate(s)	Receptor	Aliases	Other Ligands (Selection)	G Protein(s)	Expression (Major Effects)	References
<i>Hydroxycarboxylic acid receptors</i>						
Lactate	HCA ₁	GPR81, GPR104	3,5-Dihydroxybenzoid acid	G _i	Adipose tissue (antilipolytic) and low levels in the liver, skeletal muscle, and kidney	3, 20, 98, 99
3-Hydroxybutyrate (ketone body)	HCA ₂	GPR109a, HM74a, PUMA-G, NIACR1	Nicotinic acid, acifran, acipimox, MK-0354, MK-6892, and monomethyl fumarate	G _i	Adipose tissue (antilipolytic) and immune cells, including epidermal Langerhans cells, keratinocytes, intestinal epithelium, and the retinal pigment epithelium	51, 91, 104, 164, 170, 172, 179, 180, 194
3-Hydroxyoctanoate (β -oxidation intermediate)	HCA ₃	GPR109b, HM74, NIACR2	Aromatic L-amino acids, acifran, compound 3a, and compound 6o	G _i	Adipose tissue (antilipolytic), immune cells, and the colon epithelium	1, 63, 157, 162
Succinate	SUCNR1	GPR91	Compound 5 g	G _i , G _q /G ₁₁	Adipocytes, liver, heart, retinal neurons, intestine, spleen, dendritic cells, macula densa cells, kidney endothelial cells, juxtaglomerular cells (increase in renin release), and platelets	10, 53, 133, 151, 177, 182
Bile acids	TGR5	GPBAR1, BG37, GPCR19, GPR131, M-BAR, GPBA		G _s	Biliary epithelial cells, gall bladder smooth muscle (relaxation), enteroendocrine cells (increase in GLP-1 secretion), brown adipocytes (increase in energy expenditure), skeletal muscle, monocytes, macrophages, liver sinusoidal endothelial cells, enteric neurons, and astrocytes	73, 74, 76-79, 94, 107, 141, 147, 183, 189

HCA, hydroxycarboxylic acid receptor; SUCNR1, succinate receptor type 1.

tissue. Whether a similar effect can be obtained by specific antagonists of HCA₁ remains to be tested.

Ketone body 3-hydroxybutyrate. Ketone body 3-hydroxybutyrate activates the GPCR HCA₂ (also known as GPR109A) with a half-maximal concentration of 0.75 mM (170). HCA₂ is expressed in adipocytes, keratinocytes, and the intestinal and retinal pigment epithelium as well as in various immune cells, such as monocytes, neutrophils, macrophages, dendritic cells, and epidermal Langerhans cells (8, 35, 51, 85, 104, 106, 156, 164, 179, 180, 194). HCA₂ is coupled to G_i-type G proteins, and activation of the receptor in adipocytes leads to antilipolytic effects (170, 179). Since plasma levels of ketone body 3-hydroxybutyrate reach millimolar concentrations under fasting conditions, it has been suggested that the receptor mediates a negative feedback regulation during fasting and starvation (128, 158, 170). In this scenario, the increased lipolysis under fasting and starving conditions leads to increased hepatic metabolism of FFAs to ketone bodies, including 3-hydroxybutyric acid. Once ketone body 3-hydroxybutyric acid reaches millimolar concentrations in the plasma, it counterregulates lipolysis, exerting an antilipolytic effect via HCA₂. This negative feedback regulation ensures an economic use of lipids stored in adipose tissue during starvation (43, 170). The role of HCA₂ expressed in immune cells during fasting/starvation is not clear, but the receptor may mediate an anti-inflammatory effect of ketone bodies, which would promote energy conservation during starvation.

Besides its role as a ketone body receptor, HCA₂ is well known as a receptor for the antiatherogenic drug nicotinic acid (14, 164, 179, 194). Nicotinic acid has been used for decades to prevent and treat atherosclerosis (21). The prevailing view has been that the antidyslipidemic effect of nicotinic acid, a decrease in LDL-cholesterol and triglyceride levels and an increase in HDL-cholesterol levels, is responsible for its antiatherogenic activity (43). In vitro studies as well as data obtained from mice lacking HCA₂ have shown that the receptor mediates the antilipolytic and at least partially triglyceride-lowering effects of nicotinic acid (179). This was also seen in human studies (13, 88, 91) using synthetic HCA₂ agonists. However, several synthetic agonists of HCA₂ failed to decrease LDL-cholesterol and to increase HDL-cholesterol plasma levels in humans (13, 88, 91), indicating that the most beneficial antidyslipidemic effects of nicotinic acid are unlikely to involve HCA₂.

Activation of the receptor on epidermal Langerhans cells and keratinocytes is responsible for the major side effect of nicotinic acid, a cutaneous flushing reaction (7, 8, 51, 70, 104). There is increasing evidence that at least some of the beneficial effects of nicotinic acid are lipid independent (100, 195) and appear to involve anti-inflammatory effects that involve HCA₂ expressed by immune cells (101). Whether synthetic HCA₂ agonists are equivalent to nicotinic acid as antiatherogenic drugs is currently unclear.

β -Oxidation intermediate 3-hydroxyoctanoate. HCA₃ is closely related to HCA₂ but does not serve as a receptor for ketone bodies. It is present only in higher primates, and the most likely physiological agonist is the β -oxidation intermediate 3-hydroxyoctanoate (1). HCA₃ has been shown to be expressed in similar cells as HCA₂, such as adipocytes and immune cells (2, 63, 120, 164, 194, 198). Its natural ligand, 3-hydroxyoctanoate, reaches micromolar concentrations, which

are sufficient to activate the receptor under increased rates of β -oxidation (1). It has therefore been suggested that HCA₃ (similar to HCA₂) is part of a negative feedback regulation that results in the inhibition of lipolysis under conditions of increased formation of FFAs and increased FFA metabolism through β -oxidation as it occurs under fasting or starving conditions (2). As HCA₃ shares most of its expression sites with HCA₂, it has been suggested as a potential target for antiatherogenic drugs, and several synthetic HCA₃-specific agonists have been developed (12). Whether they are of clinical benefit is, however, unclear.

Succinate. The tricarboxylic acid cycle intermediate succinate is a specific agonist of a GPCR called succinate receptor 1 (SUCNR1; also known as GPR91) (53). The receptor is coupled to G_q/G₁₁ and is present in the liver, adipose tissue, retinal neurons, heart, spleen, intestine, and immune cells as well as in various renal cells, including cells of the macula densa and endothelial cells of the afferent arterioles and glomeruli (53, 151, 154, 177, 182). Studies (53, 133, 150, 177, 182) in mice lacking SUCNR1 have shown that SUCNR1 can mediate the release of renin from juxtaglomerular cells in response to elevated glucose and succinate levels, resulting in elevated blood pressure through activation of the formation of angiotensin. Especially under diabetic conditions, extracellular succinate levels are increased due to increased rates of glycolysis and tricarboxylic acid cycle activity. Besides its role in the regulation of renin secretion, SUCNR1 has also been involved in the mediation of hypoxia-induced angiogenesis in the retina, resulting in diabetic retinopathy as well as in retinopathy of prematurity. This function may be due to the accumulation of succinate under hypoxic conditions, which stimulates via SUCNR1 the formation of factors such as VEGF in retinal ganglion neurons (154). SUCNR1 can also mediate dendritic cell activation after tissue damage, which results in succinate release and the activation of SUCNR1 on dendritic cells (151). Thus, SUCNR1 appears to function as a sensor for local stress, such as tissue damage, ischemia, or hyperglycemia, which is accompanied by an increase in extracellular succinate levels (5).

α -Ketoglutarate. Another tricarboxylic acid cycle intermediate, α -ketoglutarate, has been shown to activate the GPCR GPR99 (also known as OXGR1) (53). The receptor is expressed in the kidney, placenta, smooth muscle, and testis; however, it is still unclear under which physiological or pathophysiological conditions this ligand-receptor pair may be of relevance.

Bile acids. Bile acids are produced by the liver, and their levels in the intestine and plasma depend on food intake. Besides their role in facilitating lipid uptake in the intestine, bile acids also have signaling properties and can regulate various metabolic functions. The latter effects are in part mediated by the GPCR TGR5, which is activated by the primary bile acids cholic acid and chenodeoxycholic acid with an EC₅₀ in the lower micromolar range (74, 77). Secondary bile acids, such as deoxycholic acid or lithocholic acid, are even more potent activators of TGR5 (74, 107). TGR5 is widely expressed, including in biliary epithelial cells and gall bladder smooth muscle cells (76, 94, 183), enteroendocrine cells (73, 147), and brown adipocytes and skeletal muscle cells (189). The receptor is also expressed by monocytes and macrophages, including alveolar macrophages and Kupffer cells

(74). In addition, TGR5 is found in liver sinusoidal endothelial cells, enteric neurons, and astrocytes (78, 79, 141). Activation of the receptor results in increases in cAMP levels due to preferential coupling of the receptor to G_s (74, 107).

The use of TGR5 agonists and mice lacking TGR5 has provided evidence for a variety of metabolic functions of TGR5. Two groups (108, 175) observed that mice lacking TGR5 have an increased body weight due to increased fat content, whereas another group (184) found no effect of TGR5 deficiency on body weight. Consistent with a role of TGR5 in the regulation of body weight, bile acids as well as a specific TGR5 receptor agonists were shown to induce energy expenditure, most likely by the induction of deiodinase 2 via a cAMP-mediated pathway, which results in increased mitochondrial oxidative phosphorylation and energy expenditure in brown adipose tissue and skeletal muscle due to enhanced formation of active thyroid hormone (175, 189). TGR5 also appears to play a role in the regulation of glucose metabolism, mainly due to its ability to induce GLP-1 secretion in enteroendocrine cells (73, 132, 175). In the gall bladder and bile ducts, TGR5 mediates bile acid-induced stimulation of gall bladder filling by cAMP-mediated relaxation of gall bladder smooth muscle cells (94) and modulates bile composition (76, 80). The fact that TGR5-deficient mice on a high-fat diet have an increased tendency toward the development of hepatosteatosis (184) suggests a role of TGR5 in liver function, although the receptor does not seem to be expressed in hepatocytes. However, consistent with observations in mice lacking TGR5, a specific TGR5 agonist reduced liver steatosis in high-fat diet-fed mice (175). The expression of TGR5 in monocytes and macrophages suggests a role of bile acids in the regulation of immune functions, and bile acids have indeed been shown to inhibit monocyte/macrophage activity by increasing cAMP levels (74). In atherosclerosis-prone LDL receptor-deficient mice, TGR5 expressed by bone marrow-derived cells was shown to mediate an antiatherogenic effect induced by a semisynthetic bile acid (139). Together with *in vitro* data, this strongly indicates that TGR5 expressed by plaque macrophages can mediate a reduced progression of atherosclerosis. Several synthetic or semisynthetic agonists of TGR5 are in preclinical studies as potential agents to improve glucose homeostasis and to reduce body weight, hepatic steatosis, and the progression of atherosclerosis (140, 142).

Therapeutic Potential of Metabolite GPCRs

Based on the critical role that metabolite GPCRs play not only under physiological conditions but also in diseases such as diabetes, dyslipidemia, or obesity, most of these receptors have been targets of drug development programs initiated in the pharmaceutical industry. While in some cases preclinical testing provided disappointing results, in other cases synthetic agonists showed promising results in animal models and were further developed.

HCA₂ is a receptor activated by the established drugs nicotinic acid and acipimox. As nicotinic acid appears to be a rather pleiotropic drug that does not act only through HCA₂, it is currently not clear whether synthetic agonists of HCA₂ would have beneficial effects similar to those of nicotinic acid. In fact, there is good evidence that the antidiabetic effects of nicotinic acid, such as a decrease in LDL-cholesterol and

triglycerides as well as an increase in HDL-cholesterol levels, are not mediated by the receptor but involve other, still unknown mechanisms (91). At the same time, there is increasing evidence that nicotinic acid has lipid-independent HCA₂-mediated antiatherogenic effects that appear to be mediated by HCA₂ expressed by immune cells (121).

Shortly after the discovery of GPR40 and GPR119 as receptors expressed in the endocrine pancreas as well as in enteroendocrine cells, it was suggested that agonists of the receptors would promote insulin secretion and thereby improve glucose tolerance in type 2 diabetes. While preclinical studies with specific GPR40 and GPR119 agonists provided promising data, the results of phase II clinical trials with GPR119 agonists obviously provided disappointing results (49). However, the FFA₁ (GPR40) agonist TAK-975 has recently been shown to efficaciously reduce plasma glucose levels and to be equivalent to the sulfonylurea glimepiride with significantly reduced unwanted hypoglycaemic activity (18). Among the other metabolite GPCRs, promising preclinical studies have been reported for agonists of TGR5, and clinical studies are on the way to test bile acids as TGR5 agonists in the treatment of type 2 diabetes (e.g., NCT01337440).

The field of GPCRs activated by endogenous metabolites has only recently emerged and is still in development. We may have recognized only a fraction of all metabolites sensing GPCRs and their physiological roles and therapeutic potentials. More GPCRs activated by endogenous metabolites are likely to be discovered in the future.

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