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Receptors for acylethanolamides—GPR55 and GPR119

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Abstract

Acylethanolamides are lipid substances widely distributed in the body, generated from a membrane phospholipid precursor, *N*-acylphosphatidylethanolamine (NAPE). The recent identification of arachidonoyl ethanolamide (anandamide or AEA) as an endogenous cannabinoid ligand has focused attention on acylethanolamides, which has further increased with the subsequent identification of related additional acylethanolamides with signaling function, such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA). Most of the biological functions of anandamide are mediated by the two G protein-coupled cannabinoid receptors identified to date, CB_1 and CB_2, with the transient receptor potential vanilloid-1 receptor being an additional potential target. There has been increasing pharmacological evidence for the existence of additional cannabinoid receptors, with the orphan G protein-coupled receptor GPR55 being the most actively scrutinized, and is one of the subjects of this review. The other receptor reviewed here is GPR119, which can recognize OEA and PEA. These two acylethanolamides, although structurally related to anandamide, do not interact with classical cannabinoid receptors. Instead, they have high affinity for the nuclear receptor PPARα, which is believed to mediate many of their biological effects.

Keywords

G protein-coupled receptor; Lipid ligand; Cannabinoid

1. Acylethanolamides

Acylethanolamides or fatty acid ethanolamides are lipid substances widely distributed in the body, present both in brain and various peripheral tissues, most notably in the gastrointestinal tract [1]. They are thought to be generated from a membrane phospholipid precursor, *N*-acylphosphatidylethanolamine (NAPE) by phospholipase D-mediated cleavage [2], although additional, parallel enzymatic pathways have also been identified [3,4]. NAPE has been recently identified as a hormone-like anorexic factor present in circulating blood [5], although it is not clear whether this soluble form also serves as substrate for the biosynthesis of acylethanolamides. Interest in acylethanolamides has sharply increased following the identification of arachidonoyl ethanolamide (anandamide or AEA) as the first endogenous ligand of the brain type or CB_1 cannabinoid receptor in 1992 [6]. Since that time, a number of related acylethanolamides, such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), have emerged as endogenous lipids with possible signaling and biological regulatory functions.

Most of the biological functions of anandamide and the subsequently identified 'second' endocannabinoid, 2-arachidonoylglycerol (2-AG) [7,8], as well as their plant-derived and

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synthetic cannabinoid counterparts are mediated by the two G protein-coupled cannabinoid receptors identified to date, CB_1 [9] and CB_2 [10], with the transient receptor potential vanilloid-1 (TRPV1) receptor being an additional target of anandamide [11], although one with a lower affinity than the affinity of anandamide for cannabinoid receptors. However, there has been a steady stream of pharmacological evidence for the existence of additional cannabinoid receptors [12], with the orphan G protein-coupled receptor (GPCR) GPR55 receiving most of the attention to date (see recent reviews [13–17], and is one of the subjects of the present review.

Despite its structural similarity with AEA, OEA is not a ligand at classical CB receptors. Indeed, its prominent effects as an anorexic factor that also promotes fat elimination have been convincingly linked to activation of the nuclear receptor PPARα [18]. However, some effects of OEA are independent of PPARα [19], and recent evidence indicates that OEA may also interact and produce certain biological effects via GPR119 [20], which is the second subject reviewed here. PEA also has some unique biological actions, such as its well documented analgesic and anti-inflammatory activity [21], the latter likely mediated via PPARα [22]. PEA has very low affinity for CB_1 or CB_2 receptors [23], but it may be a reasonably potent agonist for GPR55 [24].

2. GPR55

2.1. The structure of GPR55

The cloning of the human GPR55 was originally reported in 1999, when it was described as a classical intronless GPCR that maps to chromosome 2 and consists of 319 amino acids. Philogenetically, GPR55 belongs to the δ (purine) cluster of the rhodopsin family that comprises receptors for adenosine and uridine nucleotides and also contains some orphan receptors [25,26]. It displays limited amino acid sequence homology with GPR23 (30%), P2Y5 (29%), GPR35 (27%) and CCR4 (23%), homologies with CB_1 (13%) and CB_2 receptors (14%) being much lower [27]. Evidence suggesting that GPR55 may be a cannabinoid receptor first emerged in the patent literature in the early years of this decade (reviewed in [17]), and will be discussed in more detail below.

2.2. Tissue distribution of GPR55

The profile of GPR55 expression in tissues mostly comes from studies utilizing Northern blot analysis or quantitive polymerase chain reaction to detect the receptor at the message level. Thus, high levels of human GPR55 mRNA transcripts have been found in brain regions implicated in the control of memory, learning and motor functions, such as the dorsal striatum, caudate nucleus and putamen, and in several peripheral tissues, including the ileum, testis, spleen, tonsil, breast and omental adipose tissue [14,27], as well as some endothelial cell lines [28]. Rat and mouse GPR55 homologs have also been detected in other brain regions (frontal cortex, hippocampus, thalamic nuclei, brain stem and regions of the midbrain) and in peripheral tissues (jejunum, ileum, colon, adrenals and spleen) [14,24]. The significance of this distribution requires verification at the protein level and also by functional assays. So far, expression of GPR55 protein has only been documented in primary cultured mouse sensory neurons, using immunohistochemistry [29].

2.3. Pharmacology of GPR55

As for the cannabinoid-like pharmacology of GPR55, there has been a surprising variability across different studies, summarized in a recent excellent review [13] and also illustrated by the data in Table 1. There is general agreement that certain cannabinoid ligands interact with GPR55 with high affinity, and that the relative affinities of different cannabinoid ligands are distinct from the relative affinities of the same ligands established for either CB_1 or CB_2 receptors, as exemplified by a few key ligands for which results have been consistent across

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different studies and different test systems. For example, HU210, a potent synthetic agonist of CB_1 and CB_2 receptors, and JWH015, a selective CB_2 agonist, are both potent agonists at GPR55 [24,29],whereasWIN55212-2, another synthetic cannabinoid which is somewhat more potent at CB_2 than CB_1 receptors, is inactive at GPR55 [24,29–31]. Certain atypical cannabinoids that are not recognized by CB_1 or CB_2 receptors, such as abnormal cannabidiol (abnormal-CBD) and O-1602 [32], are potent agonists of GPR55 [24,28,31], whereas cannabidiol (CBD) and its analog O-1918 [33] are antagonists [24,28]. This would justify the labeling of GPR55 as 'CB_3' receptor, as long as other criteria for cannabinoid receptors are met. Such a designation, however, is not well justified when one considers that neither of the two main endocannabinoids, AEA or 2-AG, has consistent effects at GPR55. Although AEA was reported to be a potent agonist (EC_{50} of 18 nM) using GTPγS labeling and RhoA activation assays in human embryonic kidney (HEK293) cells transfected with the human GPR55 cDNA [24], it was much less potent and efficacious [29] or had no agonist activity at all in increasing intracellular calcium ($[Ca^{2+}]_i$) [34] or promoting extracellular signal-regulated kinase (ERK) phosphorylation [30,35]. 2-AG was active in increasing GTPγS labeling in one study (EC_{50} of 3 nM)[24], but was inactive in promoting calcium release or ERK phosphorylation in several other reports [29,30,34,35]. The weak activity of the two main endocannabinoids at GPR55 was further confirmed by using the PathHunter™ β-arrestin binding assay designed to evaluate GPCR-ligand pairing [36]. By measuring a signal that is specifically generated via a tagged receptor, the assay eliminates interference by endogenous receptor present in the parental cell. Using this approach, GPR55 was found to respond strongly to the CB_1 antagonists rimonabant and AM251 and also to LPI, but weakly to endocannabinoids [36]. Such findings argue against GPR55 being a cannabinoid or, more importantly, an endocannabinoid receptor, an argument also supported by the lack of significant homology with CB_1 or CB_2 receptor functional fingerprints, as defined by the alignment of amino acid residues implicated in the binding of specific cannabinoid ligands, and suggesting the absence of a cannabinoid ligand binding pocket [16]. This raises the question of what is the cognate endogenous ligand of GPR55.

2.4. Endogenous ligand(s)

Recent studies have provided strong evidence for lysophos-phatidylinositol (LPI) being such a ligand. Earlier observations have indicated that various species of LPI are present in tissues and biological fluids and can modulate a variety of cellular functions, including intracellular calcium levels [37]. LPI promoted ERK phosphorylation, a rise in $[Ca^{2+}]_i$ and GTPγS labeling in HEK293 cells transfected with hGPR55, but not in mock-transfected cells [30]. The LPI-induced rise in $[Ca^{2+}]_i$ depended on $G^{\alpha 13}$ and required activation of the small GTP-binding protein RhoA, whereas neither AEA nor 2-AG were active in this paradigm [34]. LPI also increased $[Ca^{2+}]_i$ in mouse large diameter dorsal root ganglion neurons, which express high levels of native GPR55 [29]. In this system, the effect depended on phospholipase Cβ activation via $G_{\alpha q}/G_{\alpha 12}$, and the source of the calcium released could be traced to IP_3 receptor-gated intracellular stores [29]. Additional findings indicate that among the individual molecular species of LPI, the 2-arachidonoyl species is the most potent in phosphorylating ERK and releasing intracellular calcium (EC_{50} is in the 10–100 nM range), and is thus the most likely endogenous ligand [35].While 2-arachidonoyl LPI was found to be present in the brain, representing 8.3% of all LPI species [35], its physiological functions and the mechanism of its biosynthesis remain to be clarified.

2.5. GPR55 signaling

As evidence for G protein coupling of GPR55, its agonist ligands have been consistently reported to increase [^{35}S]GTPγS binding with nanomolar potencies in membrane fractions prepared from HEK293 cells transfected with the human GPR55 gene, but not in vector-transfected control cells (hGPR55-HEK293; Table 1) [24,30]. Using peptides directed against the C termini of G protein α subunits, Ryberg and coworkers have demonstrated that GPR55

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couples to $G_{\alpha 13}$ and activates small GTPases (RhoA, cdc42 and rac1) [24]. The putative endogenous ligand of GPR55, LPI, was also found to activate $G_{\alpha 13}$ and RhoA, resulting in oscillatory release of $[Ca^{2+}]_i$ as well as further downstream activation the *n*uclear *f*actor of *a*ctivated *T* cells (NFAT) family of transcription factors, that regulate gene expression [34]. Others reported agonist-induced association ofGPR55with$G_{\alpha 12}$ and $G_{\alpha q}$, and the resulting increase in intracellular calcium from IP_3 receptor-gated stores requiring PLC activation in the case of $G_{\alpha q}$, or RhoA activation and actin polymerization in the case of $G_{\alpha 12}$, although these responses required higher, micromolar concentrations of agonists [29]. Although activation of G_{aq} and rise in $[Ca^{2+}]_i$ are generally associated with vascoconstriction, the opposite response is triggered when this happens in the endothelium, where a rise in $[Ca^{2+}]_i$ stimulates the activity of intermediate and small calcium-activated potassium channels, leading to hyperpolarization and vasorelaxation [38]. An intriguing, further complexity of GPR55 signaling has been revealed in a recent study, which provided evidence for the role of integrins in regulating anandamide signaling via CB_1 receptors and GPR55 in endothelial cells [28]. The human endothelial cell line EA.hy926 expresses both CB_1 and GPR55 receptors, each of which can be activated by anandamide. In this study, preferential activation of one or the other was found to depend on the activity status of integrins, cell surface receptors for adhesion molecules with a key role in communications between the intra- and extracellular milieu [28]. In the presence of extracellular calcium, which inhibits integrin clustering, anandamide preferentially activated $G_{i/o}$-coupled CB_1 signaling with downstream activation of spleen tyrosine kinase (Syk), which then activated NFκB and inhibited phosphoinositide 3-kinase (PI3K). Since PI3K activation plays a key role in GPR55 signaling, under these conditions GPR55 activation was suppressed. On the other hand, in the nominal absence of extracellular calcium, which results in the clustering of integrins, anandamide as well as the GPR55 ligand O-1602 evoked a rise in intracellular calcium from IP_3R-gated stores via PI3K and PLCγ activation [28]. The specific involvement of αvβ3 and α5β1 integrins was indicated by the ability of crosslinkers or neutralizing antibodies to these integrins to abrogate the GPR55-mediated calcium mobilization [28]. The presence of such alternative pathways may explain the ability of ligands that recognize both receptors to elicit opposite functional responses. For example, in human umbilical vein endothelial cells (HUVEC), anandamide acting via CB_1 receptors was reported to inhibit endothelial cell proliferation and angiogenesis [39], whereas selective activation of a non-CB_1/CB_2 receptor, possibly GPR55, by abnormal-CBD leads to increased endothelial cell migration and angiogenesis [40].

2.6. Is GPR55 the ‘endothelial’ cannabinoid receptor?

A question of particular interest is whether or not GPR55 fits the bill of the putative endothelial anandamide receptor, also dubbed the abnormal-CBD receptor for the ability of this synthetic analog to cause CB_1/CB_2-independent, endothelium-dependent vasodilation in certain vascular beds [12,15,41–43], as first documented 10 years ago in our laboratory [32,33,44]. Additional studies suggest that a putative receptor with the same or similar pharmacology is also involved in regulating microglia migration [45] and microglia-mediated neuroprotection [46], endothelial cell [40] and neutrophil migration [47], endothelial cell transformation induced by Kaposi sarcoma-associated herpesvirus infection [48], and decreasing cardiac contractility [49]. There are several shared key features of GPR55 and the abnormal-CBD receptor: with regard to the pharmacology of these sites, anandamide, but not 2-AG, appears to be an agonist ligand for both receptors, albeit with low affinity in both cases, whereas the synthetic cannabinoid WIN55212-2 is inactive at both; furthermore, abnormal-CBD and its analog, O-1602 [32], act as selective agonists, whereas CBD, which is similarly devoid of activity at CB_1 or CB_2 receptors, acts as antagonist at both receptors [24,32]. The potent, CB_1-selective antagonist rimonabant, but not its close structural analog AM251, can antagonize responses triggered via both GPR55 [29] and the abnormal-CBD receptor [32,50],

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but with an inhibitory potency one to two orders of magnitude lower than its inhibitory potency at CB_1 receptors.

Despite these similarities, there are some important differences that have been often cited as evidence for the distinct molecular nature of these two sites. First, the endothelium-dependent vasodilator effect of anandamide is pertussis toxin-sensitive [32,51], suggesting the involvement of $G_{i/o}$ proteins, whereas effects mediated by GPR55 are not, and are instead linked to $G_{\alpha12}$, $G_{\alpha13}$ or $G_{\alpha q}$ activation and rises in intracellular calcium, as discussed above. Second, there are some notable differences in the pharmacology of signaling via GPR55 versus the abnormal-CBD receptor, such as LPI being a potent agonist at the former [35] but inactive at the latter [47]. Third, the hypotensive/vasodilator actions of abnormal-CBD and its antagonism by the synthetic cannabinoid O-1918 persist in GPR55 knockout mice [31]. However, these differences are not immutable. For example, the vasodilator response to abnormal-CBD is much less sensitive to pertussis toxin than the effect of anandamide [33, 52,53], or not sensitive at all [43]. A possible explanation of such discrepant findings is that the pertussis toxin sensitivity of the effect of anandamide may reflect the involvement of CB_1/GPR55 heterodimers in these effects. Cannabinoid receptors can form heterodimers with other GPCR [54], but the possibility of their dimerization with GPR55 remains to be tested. One might speculate that to the extent such heterodimers occur, they may also account for some of the differences in the pharmacology of GPR55 and the abnormal-CBD receptor, as detected in different studies. Finally, although abnormal-CBD retained its hypotensive and mesenteric vasodilator actions in GPR knockout mice [31], this may not exclude the identity of GPR55 with the abnormal-CBD receptor. *In vivo* hypotension is a complex response with little or no relation to localized vasodilation. For example, anandamide-induced hypotension, but not mesenteric vasodilation, is absent in CB_1 receptor knockout mice [32,55]. As for the mesenteric vasodilator effect of abnormal-CBD and related ligands, only the endothelium-dependent component has been linked with a putative $G_{i/o}$-coupled GPCR [32,33], the endothelium-independent component is likely mediated by a direct activation of BK_{Ca} channels in vascular smooth muscle [56]. Unpublished observations in our laboratory indicate that mesenteric artery segments of mice, as opposed to rats, lack the endothelium-dependent component in the vasodilator response to atypical canabinoids. Thus, the possible identity of GPR55 with the putative endothelial abnormal-CBD receptor, although elusive, remains to be further tested. Another unanswered question is whether *N*-arachidonoyl-L-serine, a recently identified lipid brain constituent with vasodilator properties similar to those of abnormal-CBD [57] is also a ligand for GPR55.

2.7. GPR55 and pain sensitivity

Apart from the possible, but as yet unproven, involvement of GPR55 in cardiovascular regulation (see above), recent studies indicate its possible role in the control of pain sensitivity. GPR55−/− mice were found to lack mechanical hyperalgesia in rodent models of inflammatory and neuropathic pain [58], extending earlier observations by Lauckner and coworkers who documented abundant expression of GPR55 in large dorsal root ganglion neurons in mice and its ability to modulate the activity of these neurons [29]. Further studies are necessary to explore the potential therapeutic usefulness of selective GPR55 ligands as analgesic agents.

3. GPR119

3.1. Structure of GPR119

The human orphan receptor GPR119 was identified through a bioinformatics approach [26]. Its sequence was found to align with the earlier reported hGPCR2 receptor [59] and it is present in other mammalian species [26,60]. The 335 amino acid hGPR119 protein is encoded by an intronless gene located on chromosome X [26,59]. Philogenetically, GPR119 has been

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assigned to the MECA (***m***elanocortin; ***e***ndothelial differentiation gene; ***c***annabinoid; ***a***denosine) receptor cluster, which designates cannabinoid receptors among its closest relatives [25,26].

3.2. Tissue distribution of GPR119

GPR119 displays a relatively narrow expression pattern. The mRNA transcripts of human and rodent GPR119 have been found predominantly in pancreatic and intestinal tissues [61–63]. Rodents also express GPR119 in some brain regions [60–64]. Autoradiographic and immunohistochemical data indicate that localization of GPR119 is largely confined to a subset of cells in the pancreatic islets of Langerhans where it co-localizes with insulin [62], although another study indicates predominant GPR119 localization in pancreatic polypeptide-releasing cells [65]. In the gastrointestinal tract, GPR119 immunoreactivity was observed within villi of the small intestine where it co-localizes with glucagon-like peptide-1 (GLP-1) in proglucagon positive cells [62]. Consistent with these reports, GPR119 was also documented in the pancreatic β cell lines NIT-1, MIN6, RIN5, HIT-T15, the insulinoma cell line MIN6c4, in enterocrine L-cell models such as FRIC, mGLUTag, hNCI-H716, and in mouse L-cell primary cultures [61,62,64,66,67].

3.3. GPR119 signaling

Cells expressing GPR119 at high levels display a constitutive increase in intracellular cAMP [62], which implies coupling of GPR119 to G_s. Putative GPR119 agonists have also been reported to increase cAMP, stimulate adenylyl cyclase and enhance protein kinase A activity in cells expressing native or recombinant GPR119 [20,61–63,67,68] see also Table 2). There is also evidence for the involvement of ATP-sensitive K^+ and voltage-dependent Ca^{2+} channels in GPR119-mediated responses [66].

3.4. Pharmacology of GPR119

Because of the close philogenetic proximity of GPR119 to cannabinoid receptors, substances related to endocannabinoids were first considered as potential GPR119 ligands. Thus, using a yeast reporter assay, Overton and coworkers found that among cannabinoids only fatty acid amides induced fluorescence in cells transfected with human or mouse GPR119, with OEA being the most active, followed by PEA, and AEA displaying very weak effect [20] (Table 2). OEA was also found to stimulate cAMP production in HEK293 cells stably transfected with hGPR55, as well as in cell lines expressing native GPR119, while cells lacking GPR119 failed to respond to OEA [20,63]. Additionally, low micromolar concentrations of lysophospholipids, particularly LPC species, activated hGPR119 transgenically expressed in rat hepatoma cells (Table 2) [61].

Using high throughput screening, two groups independently identified oxadizone analogues, typified by PSN632408 [20] and AR231453 [68], as small synthetic GPR119 agonists (Table 2). These compounds were found to increase intracellular cAMP [20,62,68,69] and the secretion of insulin [62] and GLP-1 [69]. The compound AR231453 is particularly noteworthy for its nanomolar affinity for GPR119 (Table 2), while PSN632408 can also elicit some GPR119-independent effects at pharmacologically relevant concentrations [66].

3.5. Physiological function(s) of GPR119

The expression of GPR119 in pancreatic islet β-cells and intestinal enterocrine L-cells focused attention on the possible role of GPR119 in the control of glucose homeostasis and obesity. The first evidence for this came from the observation that theGPR119 agonist LPC improved glycemic control by enhancing glucose-stimulated insulin secretion from the perfused rat pancreas and that a similar effect of LPC in cultured mouse pancreatic β-cells was blunted by

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GPR119-specific siRNA [61]. The direct insulinotropic effect of GPR119 activation was subsequently documented *in vitro* using OEA [66] and AR231453 [62,68]. AR231453 was also effective in an *in vivo* model where it improved glucose tolerance by acting directly on pancreatic β-cells to enhance glucose-dependent insulin release [69]. This effect occurred in lean, diabetic, Lepr$^{db/db}$ and KKA$_y$ mice, but was entirely lost in GPR119-deficient mice [69]. The observation that AR231453 was less effective when glucose had been delivered intraperitoneally focused attention on the possible involvement of intestinal incretins in its effect. Indeed, AR231453 was found to increase GLP-1 release *in vitro*, and when it was administered to mice *in vivo*, it enhanced GLP-1 secretion after an oral glucose load and improved glucose tolerance [69]. This effect was greatly amplified when AR231453 was administered in combination with sitagliptin, an inhibitor of the GLP-1 inactivating enzyme [69]. Consistent with this observation, OEA also increases GLP-1 secretion *in vitro* and in hyperglycemic rats only after intraluminal administration, and this effect could be augmented by the FAAH inhibitor URB597 [63]. The above data suggest that orally effective GPR119 agonists and/or modulators of OEA metabolism may be used to improve glucose homeostasis.

In contrast to these observations, genetic deletion of GPR119 in mice resulted in no clearcut change in glucose homeostasis. These animals retain normal islet morphology and normal responsiveness to glucose and GLP-1, as well as normal fed/fasted glucose levels [62]. When maintained on a low fat diet, GPR119-deficient mice displayed reduced body weight and lower post-prandial GLP-1 levels relative to wild type littermates. However, these differences were no longer noticeable when the animals were on a high fat diet [64], suggesting that GPR119 is required for physiological regulation of GLP-1, but not for metabolic homeostasis. Nevertheless, the involvement of GPR119 in the physiological modulation of glucose homeostasis cannot be completely excluded, as such regulatory function may manifest under different experimental and/or pathological conditions, in animals with different genetic background, or after combined administration with sitagliptin to accentuate circulating GLP-1 levels, as reported earlier [69]. So far, basal OEA level in GPR119−/− mice has not been measured or whether it correlates with AEA, 2-AG or other lipid molecules. The elucidation of OEA–GPR119 interaction in intestinal tissue is of particular importance, because the duodenal infusion of fat has been shown to mobilize OEA in the small intestine [70] and OEA increases GLP-1 secretion from intestinal L-cells through a GPR119-dependent mechanism [63].

3.6. Does GPR119 play a role in obesity?

The idea that GPR119 may represent a potential target for the treatment of obesity comes from the de-orphanization of GPR119 as the receptor for OEA [20]. OEA had been formerly identified as a hypophagic agent that regulates feeding and body weight through activation of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα), a proposal strongly supported by the loss of OEA effects in PPARα deficient mice [18]. Like OEA, the synthetic GPR119 agonist PSN632408 was found to suppress food intake and body weight gain but, unlike OEA, it is devoid of PPARα activity [20]. On the other hand, OEA was equipotent in suppressing food intake in wild type and GPR119-deficient mice [64], which suggests that the two molecules may act through different mechanisms. Further studies will have to test whether PSN632408 and/or AR231453 retain their effects in GPR119-deficient animals. Moreover, in addition to well recognized PPARα-mediated effects such as anorexia [18,22,71], lipolysis [72] and neuroprotection [73,74], OEA has also been shown to cause a number of effects through PPARα-independent mechanisms, such as inhibition of intestinal motility [19] or reduction of visceral and inflammatory pain [75]. Whether or not such effects may be mediated via GPR119, remains to be determined.

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References

1. Borrelli F, Izzo AA. Role of acylethanolamides in the gastrointestinal tract with special reference to food intake and energy balance. Best Pract Res Clin Endocrinol Metab 2009;23(1):33–49. [PubMed: 19285259]
2. Di Marzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 1994;372(6507):686–691. [PubMed: 7990962]
3. Liu J, Wang L, Harvey-White J, et al. A biosynthetic pathway for anandamide. Proc Natl Acad Sci USA 2006;103(36):13345–13350. [PubMed: 16938887]
4. Simon GM, Cravatt BF. Anandamide biosynthesis catalyzed by the phosphodiesterase GDE1 and detection of glycerophospho-N-acyl ethanolamine precursors in mouse brain. J Biol Chem 2008;283 (14):9341–9349. [PubMed: 18227059]
5. Gillum MP, Zhang D, Zhang XM, et al. N-acylphosphatidylethanolamine, a gut-derived circulating factor induced by fat ingestion, inhibits food intake. Cell 2008;135(5):813–824. [PubMed: 19041747]
6. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258(5090):1946–1949. [PubMed: 1470919]
7. Mechoulam R, Ben-Shabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995;50(1):83–90. [PubMed: 7605349]
8. Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun 1995;215(1):89–97. [PubMed: 7575630]
9. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346(6284):561–564. [PubMed: 2165569]
10. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365(6441):61–65. [PubMed: 7689702]
11. Zygmunt PM, Petersson J, Andersson DA, et al. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 1999;400(6743):452–457. [PubMed: 10440374]
12. Begg M, Pacher P, Batkai S, et al. Evidence for novel cannabinoid receptors. Pharmacol Ther 2005;106(2):133–145. [PubMed: 15866316]
13. Ross RA. The enigmatic pharmacology of GPR55. Trends Pharmacol Sci 2009;30(3):156–163. [PubMed: 19233486]
14. Brown AJ. Novel cannabinoid receptors. Br J Pharmacol 2007;152(5):567–575. [PubMed: 17906678]
15. Hiley CR, Kaup SS. GPR55 and the vascular receptors for cannabinoids. Br J Pharmacol 2007;152 (5):559–561. [PubMed: 17704825]
16. Petitet F, Donlan M, Michel A. GPR55 as a new cannabinoid receptor: still a long way to prove it. Chem Biol Drug Des 2006;67(3):252–253. [PubMed: 16611220]
17. Baker D, Pryce G, Davies WL, Hiley CR. In silico patent searching reveals a new cannabinoid receptor. Trends Pharmacol Sci 2006;27(1):1–4. [PubMed: 16318877]
18. Fu J, Gaetani S, Oveisi F, et al. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. Nature 2003;425(6953):90–93. [PubMed: 12955147]
19. Cluny NL, Keenan CM, Lutz B, Piomelli D, Sharkey KA. The identification of peroxisome proliferator-activated receptor alpha-independent effects of oleoylethanolamide on intestinal transit in mice. Neurogastroenterol Motil. 2008
20. Overton HA, Babbs AJ, Doel SM, et al. Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents. Cell Metab 2006;3(3):167–175. [PubMed: 16517404]
21. Lambert DM, Vandevoorde S, Jonsson KO, Fowler CJ. The palmi-toylethanolamide family: a new class of anti-inflammatory agents? Curr Med Chem 2002;9(6):663–674. [PubMed: 11945130]
22. Lo Verme J, Fu J, Astarita G, et al. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol 2005;67(1): 15–19. [PubMed: 15465922]
23. Griffin G, Tao Q, Abood ME. Cloning and pharmacological characterization of the rat CB(2) cannabinoid receptor. J Pharmacol Exp Ther 2000;292(3):886–894. [PubMed: 10688601]

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24. Ryberg E, Larsson N, Sjogren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol 2007;152(7):1092–1101. [PubMed: 17876302]
25. Oh DY, Kim K, Kwon HB, Seong JY. Cellular and molecular biology of orphan G protein-coupled receptors. Int Rev Cytol 2006;252:163–218. [PubMed: 16984818]
26. Fredriksson R, Hoglund PJ, Gloriam DE, Lagerstrom MC, Schioth HB. Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives. FEBS Lett 2003;554 (3):381–388. [PubMed: 14623098]
27. Sawzdargo M, Nguyen T, Lee DK, et al. Identification and cloning of three novel human G protein-coupled receptor genes GPR52, PsiGPR53 and GPR55: GPR55 is extensively expressed in human brain. Brain Res Mol Brain Res 1999;64(2):193–198. [PubMed: 9931487]
28. Waldeck-Weiermair M, Zoratti C, Osibow K, et al. Integrin clustering enables anandamide-induced Ca2+ signaling in endothelial cells via GPR55 by protection against CB1-receptor-triggered repression. J Cell Sci 2008;121(Pt 10):1704–1717. [PubMed: 18445684]
29. Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K. GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci USA 2008;105(7):2699–2704. [PubMed: 18263732]
30. Oka S, Nakajima K, Yamashita A, Kishimoto S, Sugiura T. Identification of GPR55 as a lysophosphatidylinositol receptor. Biochem Biophys Res Commun 2007;362(4):928–934. [PubMed: 17765871]
31. Johns DG, Behm DJ, Walker DJ, et al. The novel endocannabinoid receptor GPR55 is activated by atypical cannabinoids but does not mediate their vasodilator effects. Br J Pharmacol 2007;152(5): 825–831. [PubMed: 17704827]
32. Jarai Z, Wagner JA, Varga K, et al. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci USA 1999;96(24):14136–14141. [PubMed: 10570211]
33. Offertaler L, Mo FM, Batkai S, et al. Selective ligands and cellular effectors of a G protein-coupled endothelial cannabinoid receptor. Mol Pharmacol 2003;63(3):699–705. [PubMed: 12606780]
34. Henstridge CM, Balenga NA, Ford LA, Ross RA, Waldhoer M, Irving AJ. The GPR55 ligand l-alpha-lysophosphatidylinositol promotes RhoA-dependent Ca2+ signaling and NFAT activation. FASEB J 2009;23(1):183–193. [PubMed: 18757503]
35. Oka S, Toshida T, Maruyama K, Nakajima K, Yamashita A, Sugiura T. 2-Arachidonoyl-sn-glycero-3-phosphoinositol: a possible natural ligand for GPR55. J Biochem 2009;145(1):13–20. [PubMed: 18845565]
36. Yin H, Chu A, Li W, et al. Lipid G-protein-coupled receptor ligand identification using beta-arrestin pathhunter assay. J Biol Chem. 2009
37. Corda D, Iurisci C, Berrie CP. Biological activities and metabolism of the lysophosphoinositides and glycerophosphoinositols. Biochim Biophys Acta 2002;1582(1–3):52–69. [PubMed: 12069810]
38. Busse R, Edwards G, Feletou M, Fleming I, Vanhoutte PM, Weston AH. EDHF: bringing the concepts together. Trends Pharmacol Sci 2002;23(8):374–380. [PubMed: 12377579]
39. Pisanti S, Borselli C, Oliviero O, Laezza C, Gazzerro P, Bifulco M. Antian-giogenic activity of the endocannabinoid anandamide: correlation to its tumor-suppressor efficacy. J Cell Physiol 2007;211 (2):495–503. [PubMed: 17192847]
40. Mo FM, Offertaler L, Kunos G. Atypical cannabinoid stimulates endothelial cell migration via a Gi/Go-coupled receptor distinct from CB1, CB2 or EDG-1. Eur J Pharmacol 2004;489(1–2):21–27. [PubMed: 15063151]
41. Mukhopadhyay S, Chapnick BM, Howlett AC. Anandamide-induced vasorelaxation in rabbit aortic rings has two components: G protein dependent and independent. Am J Physiol Heart Circ Physiol 2002;282(6):H2046–H2054. [PubMed: 12003810]
42. Randall MD, Kendall DA, O'Sullivan S. The complexities of the cardiovascular actions of cannabinoids. Br J Pharmacol 2004;142(1):20–26. [PubMed: 15131000]
43. Ho WS, Hiley CR. Vasodilator actions of abnormal-cannabidiol in rat isolated small mesenteric artery. Br J Pharmacol 2003;138(7):1320–1332. [PubMed: 12711633]
44. Wagner JA, Varga K, Jarai Z, Kunos G. Mesenteric vasodilation mediated by endothelial anandamide receptors. Hypertension 1999;33(1 Pt 2):429–434. [PubMed: 9931142]

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45. Walter L, Franklin A, Witting A, et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J Neurosci 2003;23(4):1398–1405. [PubMed: 12598628]

46. Kreutz S, Koch M, Bottger C, Ghadban C, Korf HW, Dehghani F. 2-Arachidonoylglycerol elicits neuroprotective effects on excitotoxically lesioned dentate gyrus granule cells via abnormal-cannabidiol-sensitive receptors on microglial cells. Glia 2009;57(3):286–294. [PubMed: 18837048]

47. McHugh D, Tanner C, Mechoulam R, Pertwee RG, Ross RA. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: evidence for a site distinct from CB1 and CB2. Mol Pharmacol 2008;73(2):441–450. [PubMed: 17965195]

48. Zhang X, Wang JF, Kunos G, Groopman JE. Cannabinoid modulation of Kaposi's sarcoma-associated herpesvirus infection and transformation. Cancer Res 2007;67(15):7230–7237. [PubMed: 17671191]

49. Ford WR, Honan SA, White R, Hiley CR. Evidence of a novel site mediating anandamide-induced negative inotropic and coronary vasodilatator responses in rat isolated hearts. Br J Pharmacol 2002;135(5):1191–1198. [PubMed: 11877326]

50. White R, Hiley CR. The actions of some cannabinoid receptor ligands in the rat isolated mesenteric artery. Br J Pharmacol 1998;125(3):533–541. [PubMed: 9806337]

51. White R, Hiley CR. A comparison of EDHF-mediated and anandamide-induced relaxations in the rat isolated mesenteric artery. Br J Pharmacol 1997;122(8):1573–1584. [PubMed: 9422801]

52. Su JY, Vo AC. 2-Arachidonylglyceryl ether and abnormal cannabidiol-induced vascular smooth muscle relaxation in rabbit pulmonary arteries via receptor-pertussis toxin sensitive G proteins-ERK1/2 signaling. Eur J Pharmacol 2007;559(2–3):189–195. [PubMed: 17292352]

53. Kozlowska H, Baranowska M, Schlicker E, Kozlowski M, Laudanski J, Malinowska B. Identification of the vasodilatory endothelial cannabinoid receptor in the human pulmonary artery. J Hypertens 2007;25(11):2240–2248. [PubMed: 17921818]

54. Mackie K. Cannabinoid receptor homo- and heterodimerization. Life Sci 2005;77(14):1667–1673. [PubMed: 15978631]

55. Ledent C, Valverde O, Cossu G, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 1999;283(5400):401–404. [PubMed: 9888857]

56. Godlewski G, Offertaler L, Osei-Hyiaman D, et al. The endogenous brain constituent N-arachidonoyl l-serine is an activator of large conductance Ca2+-activated K+ channels. J Pharmacol Exp Ther 2009;328(1):351–361. [PubMed: 18923087]

57. Milman G, Maor Y, Abu-Lafi S, et al. N-arachidonoyl l-serine, an endocannabinoid-like brain constituent with vasodilatory properties. Proc Natl Acad Sci USA 2006;103(7):2428–2433. [PubMed: 16467152]

58. Staton PC, Hatcher JP, Walker DJ, et al. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. Pain 2008;139(1):225–236. [PubMed: 18502582]

59. Takeda S, Kadowaki S, Haga T, Takaesu H, Mitaku S. Identification of G protein-coupled receptor genes from the human genome sequence. FEBS Lett 2002;520(1–3):97–101. [PubMed: 12044878]

60. Overton HA, Fyfe MC, Reynet C. GPR119, a novel G protein-coupled receptor target for the treatment of type 2 diabetes and obesity. Br J Pharmacol 2008;153:S76–S81. [PubMed: 18037923]

61. Soga T, Ohishi T, Matsui T, et al. Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor. Biochem Biophys Res Commun 2005;326(4):744–751. [PubMed: 15607732]

62. Chu ZL, Jones RM, He H, et al. A role for beta-cell-expressed G protein-coupled receptor 119 in glycemic control by enhancing glucose-dependent insulin release. Endocrinology 2007;148(6):2601–2609. [PubMed: 17289847]

63. Lauffer LM, Iakoubov R, Brubaker PL. GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. Diabetes 2009;58(5):1058–1066. [PubMed: 19208912]

64. Lan H, Vassileva G, Corona A, et al. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. J Endocrinol 2009;201(2):219–230. [PubMed: 19282326]

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65. Sakamoto Y, Inoue H, Kawakami S, et al. Expression and distribution of Gpr119 in the pancreatic islets of mice and rats: predominant localization in pancreatic polypeptide-secreting PP-cells. Biochem Biophys Res Commun 2006;351(2):474–480. [PubMed: 17070774]
66. Ning Y, O'Neill K, Lan H, et al. Endogenous and synthetic agonists of GPR119 differ in signalling pathways and their effects on insulin secretion in MIN6c4 insulinoma cells. Br J Pharmacol 2008;155 (7):1056–1065. [PubMed: 18724386]
67. Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM. Glucose sensing in L cells: a primary cell study. Cell Metab 2008;8(6):532–539. [PubMed: 19041768]
68. Semple G, Fioravanti B, Pereira G, et al. Discovery of the first potent and orally efficacious agonist of the orphan G-protein coupled receptor 119. J Med Chem 2008;51(17):5172–5175. [PubMed: 18698756]
69. Chu ZL, Carroll C, Alfonso J, et al. A role for intestinal endocrine cell-expressed g protein-coupled receptor 119 in glycemic control by enhancing glucagon-like peptide-1 and glucose-dependent insulinotropic peptide release. Endocrinology 2008;149(5):2038–2047. [PubMed: 18202141]
70. Schwartz GJ, Fu J, Astarita G, et al. The lipid messenger OEA links dietary fat intake to satiety. Cell Metab 2008;8(4):281–288. [PubMed: 18840358]
71. Fu J, Kim J, Oveisi F, Astarita G, Piomelli D. Targeted enhancement of oleoylethanolamide production in proximal small intestine induces across-meal satiety in rats. Am J Physiol Regul Integr Comp Physiol 2008;295(1):R45–R50. [PubMed: 18434444]
72. Guzman M, Lo Verme J, Fu J, Oveisi F, Blazquez C, Piomelli D. Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-alpha). J Biol Chem 2004;279(27):27849–27854. [PubMed: 15123613]
73. Sun Y, Alexander SP, Garle MJ, et al. Cannabinoid activation of PPAR alpha; a novel neuroprotective mechanism. Br J Pharmacol 2007;152(5):734–743. [PubMed: 17906680]
74. Galan-Rodriguez B, Suarez J, Gonzalez-Aparicio R, et al. Oleoylethanolamide exerts partial and dose-dependent neuroprotection of substantia nigra dopamine neurons. Neuropharmacology 2009;56(3): 653–664. [PubMed: 19070629]
75. Suardiaz M, Estivill-Torrus G, Goicoechea C, Bilbao A, Rodriguez de Fonseca F. Analgesic properties of oleoylethanolamide (OEA) in visceral and inflammatory pain. Pain 2007;133(1–3):99–110. [PubMed: 17449181]

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Table 1

Pharmacological profile of compounds tested as GPR55 ligands.

Compound	Cell type	Measured response [references]					
		$[^{35}S]GTP\gamma S$	$[Ca^{2+}]_i$ mobilization	pERK 1/2	RhoA	NAFT	β-Arrestin [36]
Cannabinoids							
AEA	hGPR55-HEK293	EC_{50} 18 nM [24]	5 μM [29]; no effect [32,35]	No effect [30,35]	1 μM [24]	-	Very weak
	EA.hy926	-	EC_{50} 7.3 μM [28]	10 μM [28]	-	10 μM [28]	-
Meth-AEA	hGPR55-HEK293	-	5 μM [29]	-	-	-	-
	EA.hy926	-	EC_{50} 10.6 μM [28] 5 μM [29]	-	-	-	-
OEA	hGPR55-HEK293	EC_{50} 440 nM [24]	-	No effect [30]	-	-	-
PEA	hGPR55-HEK293	EC_{50} 3–4 nM [24]	No effect [29]	No effect [30]	-	-	-
Virodhamine	hGPR55-HEK293	EC_{50} 10–12 nM [24]	No effect [29]	No effect [30]	-	-	-
2-AG	hGPR55-HEK293	EC_{50} 3 nM [24]	No effect [29,32,35]	No effect [30,35]	-	-	No effect
Noladin ether	hGPR55-HEK293	EC_{50} 10–11 nM [24]	-		-	-	
abnormal-CBD	hGPR55-HEK293	EC_{50} 2.5 nM to 2.8 μM [20,24, 31]	No effect [29]	No effect [30]	-	-	No effect
O1602	hGPR55-HEK293	EC_{50} 2.5–13 nM [24,31]	No effect [35]	No effect [30]	1 μM [24]	-	No effect
CBD	hGPR55-HEK293	IC_{50} 350 nM [24]	No effect [29]	-	Antagonist-10 μM [6]	-	-
	EA.hy926	-	10 μM [28]	-	1 μM [24]	-	No effect
O1918	EA.hy926	-	Antagonist [28]	-	-	-	-
Δ^9THC	hGPR55-HEK293	EC_{50} 8 nM [24]	5 μM [29]	5 μM [29]; No effect [30]	5 μM [29]	-	Weak
	Mouse DRG	-	5 μM [29]	-	-	-	-
HU210	hGPR55-HEK293	EC_{50} 26–33 nM [10,24]	-	No effect [30]	-	-	No effect
CP55940	hGPR55-HEK293	EC_{50} 5–7 nM [24]	No effect [29,35]; antagonist [32]	No effect [30]	-	-	No effect
WIN55212-2	hGPR55-HEK293	No effect [24,31]	No effect [29]	No effect [30]	No effect [24]	-	-

Compound	Cell type	Measured response [references]					
		[^{35}S]GTPγS	$[Ca^{2+}]_i$ mobilization	pERK 1/2	RhoA	NAFT	β-Arrestin [36]
AM251	hGPR55-HEK293	EC_{50} 39 nM [24]	-	-	-	-	EC_{50} 2.7 μM
Rimonabant	hGPR55-HEK293	EC_{50} 600 nM [24]	-	No effect [30]	-	-	EC_{50} 9.3 μM
	Mouse DRG	-	Antagonist-2 μM [29]	-	-	-	-
JWH015	hGPR55-HEK293	EC_{50} 4 nM [24]	3 μM [29]	3 μM [29]	3 μM [29]	-	-
	Mouse DRG	-	3 μM [29]	-	-	-	-
Lysophospholipids							
LPI	hGPR55-HEK293	EC_{50} 1 μM [30]	EC_{50} 49 nM to 1 μM [30,32]	EC_{50} 200 nM [30]	1 μM [32]	1 μM [32]	EC_{50} 3.6 μM
	EA.hy926	-	10 μM [28]	-	-	-	-
	Mouse DRG	-	3 μM [29]	-	-	-	-
2-AG-LPI	hGPR55-HEK293	-	EC_{50} 30 nM [35]	EC_{50} 1 μM [35]	-	-	-

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Table 2

Pharmacological profile of compounds tested as GPR119 ligands.

Compound	Cell type	Measured response	Effect, EC_{50} value	[Reference]
Cannabinoids				
Anandamide	hGPR119-yeast	Fluorimetric assay	very weak	[57]
OEA	hGPR55-HEK293	↑cAMP	EC_{50}2.9 μM	[57]
	hGPR55-yeast	Fluorimetric assay	EC_{50}3.2 μM	[57]
	mGPR55-yeast	Fluorimetric assay	EC_{50}2.9 μM	[57]
PEA	hGPR55-yeast	Fluorimetric assay	EC_{50}3.2 μM, low efficacy	[57]
2-AG	hGPR55-yeast	Fluorimetric assay	no effect	[57]
CP5594	hGPR55-yeast	Fluorimetric assay	no effect	[57]
WIN55212-2	hGPR55-yeast	Fluorimetric assay	no effect	[57]
JWH133	hGPR55-yeast	Fluorimetric assay	no effect	[57]
Lysophospholipids				
Oleoyl LPC	hGPR119-RH7777	↑cAMP	EC_{50}1.5 μM	[58]
	hGPR55-yeast	Fluorimetric assay	EC_{50} >30 μM	[57]
	mGPR55-yeast	Fluorimetric assay	EC_{50} >30 μM	[57]
Palmitoyl LPC	hGPR119-RH7777	↑cAMP	EC_{50}1.6 μM	[58]
Stearoyl LPC	hGPR119-RH7777	↑cAMP	EC_{50}3.3 μM	[58]
LP-ethanolamine	hGPR119-RH7777	↑cAMP	EC_{50}5.7 μM	[58]
LPI	hGPR119-RH7777	↑cAMP	EC_{50}5.7 μM	[58]
Synthetic ligands				
PSN632408	hGPR55-HEK293	↑cAMP	EC_{50}1.9 μM	[57]
	hGPR55-yeast	Fluorimetric assay	EC_{50}5.6 μM	[57]
	mGPR55-yeast	Fluorimetric assay	EC_{50}7.9 μM	[57]
AR231453	hGPR55-HEK293	↑cAMP	EC_{50}5.7 nM	[59]
	HIT-T15	↑cAMP	EC_{50}4.7 nM	[59]
	HIT-T15	insulin release	EC_{50}3.5 nM	[59]
	GLUtag	↑cAMP	EC_{50}4.3 nM	[59]
	GLUtag	GLP-1 release	EC_{50}56 nM	[59]