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GPR55: metabolic help or hindrance?

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Abstract

Since the discovery of the lysophospholipid-sensitive receptor GPR55, hopes have been raised that targeting this GPCR may represent a novel approach for the treatment of metabolic disorders. Here, we discuss conflicting evidence surrounding GPR55 physiology and highlight its potential as a novel target for the treatment of obesity and diabetes.

Keywords

GPR55, LPI, obesity, diabetes, metabolism

Cannabinoid therapeutics for obesity

Excessive intake of rich, non-nutritious foods can result in metabolic disorders such as obesity and related comorbidities, including type 2 diabetes mellitus (T2DM). As obesity levels continue to rise, development of new therapeutics is crucial for the slowing or reversal of this escalating epidemic.

One physiological system that may be therapeutically exploited to control obesity is the endocannabinoid system (ECS). This system classically consists of two cannabinoid receptors (CB1 and CB2), two major endogenous ligands (2-arachidonyl glycerol (2-AG) and anandamide (AEA)) and the enzymes involved in the synthesis and breakdown of these ligands. The ECS plays a crucial role in both the central and peripheral control of body weight and food intake, affecting insulin sensitivity, glucose homeostasis and fat accumulation [1]. Cannabinoid agonists increase the desire for and consumption of non-nutritious foodstuffs, an observation that led to development of a CB1 antagonist (Rimonabant) for treating obesity. Rimonabant, while clinically efficacious and initially hailed as a potential blockbuster, was removed from clinical use after only two years, due to adverse psychological effects, including suicidal ideation.

GPR55: a cannabinoid and lipid sensitive receptor

The description of a third cannabinoid-sensitive receptor in 2007 called G-protein-coupled receptor 55 (GPR55), brought the ECS again to the forefront with the hope of generating anti-obesity drugs that lacked the adverse effects of Rimonabant. GPR55 is a classical rhodopsin-like seven transmembrane GPCR that despite showing cannabinoid sensitivity, shares less than 15% sequence identity with the cannabinoid receptors and lacks the classical cannabinoid binding pocket [2]. Human GPR55 shares approximately 80% sequence identity with rat and mouse orthologs and is found at high levels in human spleen, intestines, stomach and brain [2]. Research into GPR55 expanded rapidly but erratically, resulting in a rather confusing pharmacological profile. GPR55 certainly displays sensitivity to diverse cannabinoid compounds, including Rimonabant, but the most consistently described ligand is the endogenous lipid, lysophosphatidylinositol (LPI) [2]. Following a recent nomenclature review of lysophospholipid-sensitive receptors, GPR55 has been provisionally named LPI₁. It is now understood that several of the previously described physiological effects of LPI are mediated via GPR55 [2]. GPR55 couples to G α_{13} G-proteins to activate the small GTPase RhoA, mobilise Ca²⁺ release from intracellular stores and activate multiple transcription factors [2].

Species-specific effects of GPR55 and LPI on body weight

Although studies are rather scarce, recent evidence suggests that GPR55 might play a role in regulating human body weight. In a cohort of Japanese women, a Gly195Val missense polymorphism of GPR55 was associated with increased incidence of anorexia nervosa [3]. The Gly195Val mutation appeared to reduce -

but not abolish - GPR55 function, although effects on receptor expression were not investigated [3]. A separate study investigated GPR55 expression and circulating levels of LPI in lean, obese and diabetic individuals. GPR55 in visceral fat correlated with higher body fat percentage and overall weight, with the highest GPR55 levels recorded in diabetic patients [4]. Circulating plasma LPI levels also correlated with body fat percentage and overall weight [4]. Interestingly, these associations were strong in female participants but weak or absent in males. There is, as yet, no explanation for the difference, although sexual dimorphism is not uncommon in the regulation of energy homeostasis. Furthermore, LPI induced Ca^{2+} release in cultured primary adipocytes and increased the expression of genes involved in fat deposition in explants of visceral fat [4]. In summary, clinical and in vitro studies suggest that GPR55 activation by LPI might be linked to increased weight and fat deposition in humans, and pharmacological blockade of GPR55 may be beneficial in controlling excessive weight gain.

Studies utilising GPR55^{-/-} mice, however, report different effects of GPR55 on body weight and insulin sensitivity. Genetic deletion of GPR55 appears to have no effect on overall body weight [5-7]. However, one of these studies found increased fat deposition and insulin resistance in GPR55^{-/-} mice due to decreased physical activity, while no significant change in food intake or body weight was observed in these animals [6]. Furthermore, Moreno-Navarrete et al. [4] report that ob/ob mice had lower levels of GPR55 mRNA and protein in white adipose tissue compared to WT littermates, and rats fed a “high fat” diet had lower GPR55 expression compared to rats on a “low fat” diet.

Collectively, these findings suggest that GPR55 plays different metabolic roles in distinct species, making the translation between rodents and human problematic. As yet, no clear disparity in pharmacology or signalling between rodent and human GPR55 has been described, making these findings difficult to reconcile. However, whole-body GPR55 knockout mice may have numerous compensatory changes in other genes that influence fat deposition and metabolism, leading to contradictory results. Alternatively, GPR55 knockout may exert effects on other systems that ultimately influence adipose physiology, such as adipose inflammation, a potential conflicting factor in the Meadows et al. study [6]. Selective GPR55 antagonists have recently become available, and these will enable more thorough elucidation of the role of GPR55 in fat deposition (Box 1).

GPR55 and LPI effects on pancreatic function

Pancreatic beta cells are critical for maintaining proper insulin levels and glucose homeostasis. Thirty years ago, LPI was shown to stimulate insulin release from cultured pancreatic islets [8], but it took almost 20 years to identify GPR55 as the receptor involved. It is now known that GPR55 is expressed in rodent and human islets and activation of the receptor increases insulin release from cultured rodent cells [9, 10]. Furthermore, GPR55 agonists were shown to decrease glucose levels and increase plasma insulin levels [9] in rodents. This small

number of rodent studies suggests that GPR55 may be therapeutically relevant for insulin sensitivity and glucose homeostasis, however further research in this area is required.

GPR55 and LPI effects on the gastrointestinal system

GPR55 is expressed in the human gastrointestinal (GI) tract [2], but its role in the gut remains largely unknown. In rodent, GPR55 is expressed in distinct regions of the gut including the duodenum, jejunum, ileum and colon. It is known that GPR55 is expressed not only on the GI endothelial cells but also on the myenteric neurons of the colon, suggesting that it may play a role in GI motility. Indeed, activation of GPR55 appears to inhibit gut motility [11]. Furthermore, GPR55 also regulates intestinal inflammation. GPR55 antagonists reduce intestinal inflammation in *in vivo* rodent models [12]. These few studies raise the possibility that GPR55 modulators may represent novel therapeutics for intestinal disorders; however more work is required to elucidate the role of GPR55 in GI physiology.

GPR55 and LPI effects on cancer

While research into the GPR55-LPI signalling axis in metabolism is gradually coming to fruition, it has already been shown to exert multifarious effects on cancer. In the 1980s, LPI was shown to be released from thyroid cells and fibroblasts that were transformed with the oncogene Ras. LPI released from cancer cells can drive cell proliferation via autocrine activation of GPR55 on the cell surface, which is a significant finding since women with ovarian cancer have high plasma LPI levels [13]. GPR55 mRNA is expressed in tumors from diverse human cancers ranging from brain to pancreatic cancer and is expressed more highly in breast and pancreatic tumors of high histological grade compared to low-grade and healthy tissue [14]. GPR55 appears to be a causative factor, as over-expression of GPR55 in cancer cell lines leads to increased proliferation whereas siRNA knockdown of GPR55 renders cells less proliferative [14]. Taken together, these studies suggest that increased GPR55 expression may induce cancer progression. In agreement with this hypothesis, it has recently been shown that GPR55 antagonists (See text box) inhibit migration and adhesion of colon cancer cells and decrease liver metastasis in mice [15].

Concluding remarks

Given the increasing global incidence of metabolic disorders, new drugs that lower body weight and improve glucose tolerance are desperately needed. While we still have a long way to go, GPR55 might be an interesting target to explore, given its expression in numerous metabolically important tissues in humans (Figure 1). However, prudence is required in extrapolating findings from current rodent models, given the disparity in results between human and rodent weight gain following GPR55 perturbation. A more thorough understanding of the

178 commonalities and differences of the GPR55-LPI signalling axis between human
179 and rodents will be vital to allow for the transition of these compounds into
180 clinical development.
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Text Box: New GPR55 antagonists

Cannabidiol (CBD), a constituent of *Cannabis sativa* plant, was one of the first described GPR55 antagonists. However, CBD is not selective for GPR55 and has proved inconsistent in blocking GPR55-mediated agonist effects *in vitro*, across different research groups. Recent studies have identified more selective and chemically distinct GPR55 antagonists, ML193 and CID16020046, through systematic drug-screening approaches. ML193 has nanomolar potency at GPR55 and more than 145-fold selectivity over GPR35, its phylogenetic homologue. CID16020046 can antagonise a chemically diverse range of GPR55 agonists and has potency is in the high nanomolar range. These tools have already been exploited in a small number of *in vivo* studies to reduce intestinal inflammation [12] and LPI-induced angiogenesis [16] and will be crucial for defining the role of GPR55 in metabolic and other physiological systems.

Figure 1: Comparison of the expression and function of GPR55 in rodent and human metabolic tissues

The figure summarises our current understanding of the similarities and discrepancies (highlighted in **bold**) between rodent and human GPR55 expression and function, in metabolically important tissues.

GPR55 - Rodent

- GPR55 expressed in many brain regions, including the hypothalamus
- **GPR55^{-/-} mice have a normal body weight**

- GPR55 expressed in islets (β -cells)
- GPR55 agonists - $\uparrow$ insulin release
- $\downarrow$ plasma glucose

- GPR55 expressed in white adipose tissue (WAT)
- **$\downarrow$ WAT GPR55 found in ob/ob mice**
- **Rats fed high fat diet exhibit $\downarrow$ GPR55**

- GPR55 expressed in stomach, intestines and myenteric neurons
- GPR55 agonists slow GI transit
- GPR55 antagonists $\downarrow$ intestinal inflammation

- GPR55 expressed in liver
- Function currently unknown

Brain

Pancreas

Adipose Tissue

GI tract

Liver

GPR55 - Human

- GPR55 expressed in many brain regions, including the hypothalamus
- **GPR55 mutation (loss of function) associates with $\uparrow$ incidence of anorexia nervosa**

- GPR55 expressed in islets (β -cells)
- GPR55 agonists - $\uparrow$ insulin release

- GPR55 in visceral fat $>$ subcutaneous fat
- **$\uparrow$ GPR55 associates with $\uparrow$ weight**
- $\uparrow$ plasma LPI associates with $\uparrow$ weight
- GPR55 agonists $\uparrow$ fat deposition

- GPR55 expressed in stomach, intestines and myenteric neurons
- Function currently unknown

- GPR55 expressed in liver
- Function currently unknown