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RESEARCH ARTICLE

Advances in the Physiology of GPR55 in the Central Nervous System

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Abstract: ***Background*:** The G protein-coupled receptor 55 (GPR55) is a mammalian orphan receptor that awaits a formal classification. There are an increasing number of reports directed to know the physiology and pathophysiology of this receptor. Lamentably, its functions in the central nervous system (CNS) have been scarcely elucidated.

***Methods*:** A bibliographic search in PubMed database about GPR55 actions in the CNS was made. The information was grouped for brain structures to facilitate the interpretation. Finally, we constructed a schematic representation of the current knowledge about the potential participation of GPR55 in some physiological and pathophysiological events.

***Results*:** Seventy nine papers were included in the review. Only few of them showed data about GPR55 (mRNA/protein) expression in multiple brain areas. The rest showed findings in different preparations both *in vitro* and *in vivo* conditions that allowed us to speculate a potential activity of GPR55 in the different brain areas.

***Conclusion*:** GPR55 mRNA is expressed in several brain areas as the hippocampus, hypothalamus, frontal cortex and cerebellum; but due to the lack of information, only some speculative information about its function in these regions has been suggested. Therefore, this review provide relevant information to motivate further research about GPR55 physiology/pathophysiology in the CNS.

Keywords: GPR55, endocannabinoid system, central nervous system, lysophosphatidylinositol, procedural memory.

INTRODUCTION

The G protein-coupled receptor 55 (GPR55) is activated by endocannabinoids and lysophosphatidylinositol [1-3] (LPI). It is controversial whether endocannabinoids can fully activate GPR55 [1, 4] (Table **1**), whereas other non-cannabinoid lipids, *i.e*. LPI do it [3, 4]. At the moment, the nomenclature of GPR55 is discussed by the cannabinoid receptor subcommittee of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification [5]. In this context, the proposal of GPR55 as the cannabinoid receptor type 3 is still under discussion [1-3, 6]. Many studies have reported great functional interaction between GPR55 and the classic cannabinoid receptors CB_1/CB_2 [6-8], despite the fact that GPR55 has poor amino acid sequence homology with CB_1 (13.5) and CB_2 (14.4%) [6].

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This finding is not surprising since other systems also show a great interaction in spite of the low homology in their receptors. For example: the serotonin receptor 5-HT3 which shares less than 10% of the amino acid sequences with the other six members of the family [9]. It is the only member of this receptor family associated with a cationic channel instead of metabotropic proteins. Thus, the low homology between GPR55 and the classic cannabinoid receptors is not enough to discard GPR55 as a cannabinoid receptor.

As mentioned above, the lack of homology may explain the differences in the signaling system and downstream cascade associated with GPR55. CB_1 and CB_2 are coupled to Gi/o-proteins which inhibit the adenylyl cyclase and increase the activation of the mitogen-activated protein kinase (CB_1 receptor also regulates the activity of Ca^{2+} and K^+ channels) [10] and consequently, they have been related with cellular activity inhibition (*e.g*. neural inhibition of neurotransmitters release). On the other hand, there are experimental evidences that GPR55 promotes the outflow of calcium from intracellular stores *via* phospholipase C activation [11], and accordingly, cellular excitation (*e.g*. neural facilitation of neurotransmitters release). The functionally opposite

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signaling pathways from CB_1/CB_2 and GPR55 lead to potential pharmacological consequences; for example: as some CB1 antagonists/inverse agonists (*e.g*., AM251) have activity as GPR55 agonists (Table **1**), it is possible that some effects induced by cannabinoids and blocked with these antagonists/ inverse agonists involve GPR55 instead or additionally to the classic CB_1 activity. If so, the protagonist role of CB_1 receptors within the endocannabinoid system, widely reported in scientific literature, should be opened to further examination and revaluation.

The function of GPR55 receptors in the periphery have been extensively studied and involved in different processes, for example: vasodilatation endothelium-dependent [8], cellular proliferation and migration [12], bone dynamics [13], energy balance [14], gastrointestinal processes [15], inflammation and pain [16], among others. Nevertheless, in the central nervous system (CNS), few recent studies suggest that GPR55 could be modulating procedural memory [17], motor coordination [18], anxiety and hippocampal release of glutamate [19]. However, the physiological implications of these findings are unclear. In this review, we summarize the current knowledge about the physiology of GPR55 in the CNS to explore its potential physiologic and therapeutic actions and to promote further investigation related with this receptor.

PHARMACOLOGY OF THE ENDOCANNABINOID SYSTEM AND GPR55

The endocannabinoids are lipids involved in neuro-modulation and celullar control within the body. They represent part of an ancient lipid-system of homeostatic control which has differentially evolved in the eukaryotes [20]. The enzymes for the metabolism of some elements of the endocannabinoid system seem to be as ancient as the origin of the *Eukarya* domain [20]. Later, organisms from *Animalia* express the CB_1 receptor or at least a CB_1-like receptor, but only vertebrates express CB_2 receptors [20]. Interestingly, GPR55 and transient receptor potential cation channel (TRPV1), which are also activated by endo-cannabinoids [21], appear only in the mammalians [20]. The endocannabinoid system as known today (in human beings) is probably an outcome of several million years of evolution.

Table 1. Affinity of several cannabinoids and lysophospha-tidylinositol for CB_1, CB_2 and GPR55.

Compound	CB_1	CB_2	GPR55
Anandamide	[1] 7.4 pEC_{50}	[1] 7.6 pEC_{50}	[1] 7.7 pEC_{50}
2-AG	[1] 6.2 pEC_{50}	[1] 6.2pEC_{50}	[1] 8.5 pEC_{50}
Virhodamide	[1] 5.5 pEC_{50}	[1] 6.4 pEC_{50}	[1] 7.9 pEC_{50}
Noladin-ether	[1] 7.5 pEC_{50}	[1] <4.5 pEC_{50}	[1] 8.0 pEC_{50}
NADA	[22] 6.6 pEC_{50}	[22] 4.9 pEC_{50}	N.D.
LPI	[23] <4.5 pEC_{50}	N.D.	[24, 25] 5.5-7.3 pEC_{50}
Δ9-THC	[1] 8.2 pEC_{50}	[1] 9.4pEC_{50}	[1] 8.1 pEC_{50}
Cannabidiol	[1] <4.5 pIC_{50}	[1] <4.5 pIC_{50}	[1] 6.3 pIC_{50}
AM251	[1] 8.1 pIC_{50}	[1] 5.5 pIC_{50}	[1, 25] 7.2-7.4 pEC_{50}

Data taken from: Ryberg *et al*., 2007; [1] Bisogno *et al*., 2000; [22] Kapur *et al*., 2009; [23] Southern *et al*., 2013 [24]; Henstridge *et al*., 2010 [25]. 2-AG, 2-araquidonylglicerol; NADA, N-araquidonyldopamine; LPI, lysophosphatidylinositol.

The endocannabinoid system is integrated by: (i) two well characterized cannabinoid G-protein coupled receptors CB_1 and CB_2; (ii) several molecules with agonistic activity on these receptors, *i.e*., anandamide, 2-araquidonylglicerol (2-AG), noladin ether, N-araquidonyldopamine (NADA), virhodamide and compounds endocannabinoid-like as palmitoylethanolamide (PEA) among others; (iii) the machinery involved in the synthesis and clearance of them; and (iv) the respective genes encoding for all the molecules in this system that are proteins [20, 26].

It is important to highlight that the CB_1 and CB_2 receptors do not explain the whole effects of cannabinoids in the body [8, 27, 28]. Apart from the CB_1 and CB_2 receptors, cannabinoids exert their effects by a spread number of: (i) ion channels as TRPV1 [21, 29], TRPV3 and TRPV4 [30], 5-HT3 [31] and Na+ and K+ [32]; (ii) nuclear receptors as peroxisome proliferator-activated receptors (PPAR) [33] and (iii) metabotropic cannabinoid putative receptors GPR18, GPR55, among others [34, 35].

In past years, GPR55 was proposed as the novel cannabinoid receptor type 3 (CB_3) [1]. Nevertheless, the low structural similitude with the classical cannabinoid receptors [36], the lack of selectivity of an endogenous cannabinoid agonist (see Table **1**) and the activity of the non-cannabinoid compound LPI as a full agonist [2] suggest that GPR55 may be a receptor for non-cannabinoid lipids [3, 37]. However, considering the high potency by which some endo-cannabinoids and endocannabinoid-like compounds activate GPR55 (an interaction sometimes higher than this for CB_1; Table **1**), the establishment of GPR55 as a non-cannabinoid receptor should obligate to re-evaluate our definitions to characterize the components of the endocannabinoid system. Interestingly, the proposed GPR55 endogenous agonist (the 2-arachidonyl LPI) may be transformed to the endo-cannabinoid 2-AG by the LysoPLC enzyme [38]. LysoPLC enzyme has been purified from homogenate of pig brain suggesting that its functions may be at a global level in the brain. At the end of the day, all these lipid components belong to the same global system of lipid cellular control.

Independently of this discussion, the cannabinoid CB_1 and CB_2 receptors are highly functional and structural related with GPR55 [7, 38]. Supporting this, many tissues which are known to be importantly controlled by CB_1 or CB_2 receptors seem to express functional GPR55. One clear example of this relationship is the cardiovascular system. In the cardio-vascular system CB_1 and GPR55 seem to work together to negative control the sympathetic outflow *via* noradrenaline/ ATP inhibition and endothelial vasodilatation, respectively [8]. Indeed, $GPR55^{-/-}$ knockout mice developed ventricular dysfunction [39], while $CB_1^{-/-}$ knockout developed important increases in the ventricular end-dyastolic pressure and in the weight of heart, which drive to a marked increase of mortality due to heart failure [40].

Waldeck-Weiermair *et al*. [41] showed that, under certain conditions, endothelial CB_1 receptors may block the

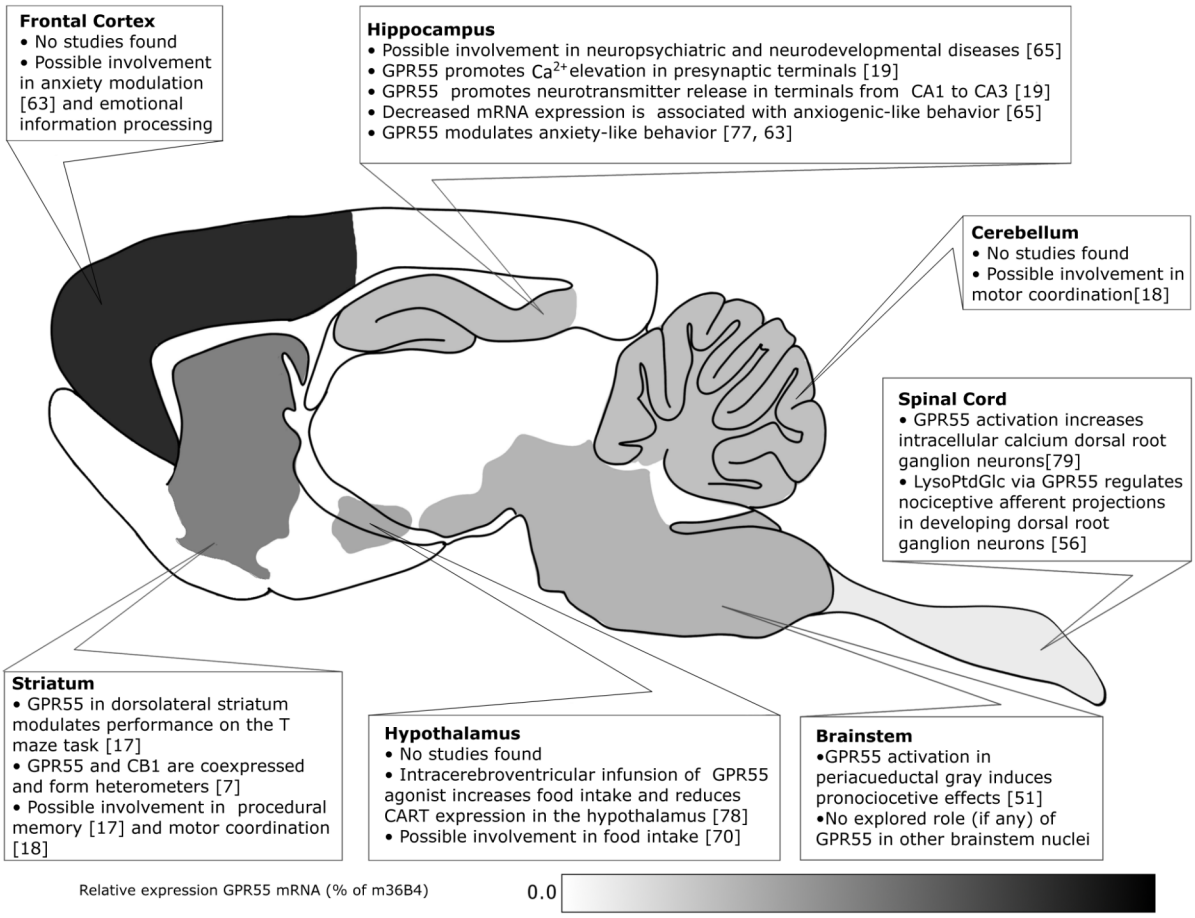

Fig. (1). Schematic representation of the relative GPR55 mRNA expression (% of ribosomal M36b4) in the central nervous system. Data taken from Ryberg *et al*. [1]. Note that although the diagram represents a rodent brain, information from the textboxes comes from several animal models (*i.e.*, rat, mouse, monkey, *etc*). Lighter shades of gray indicate lower receptor expression while darker shades indicate higher receptor expression. Structures in white represent lack of information about GPR55 expression.

downstream cascade associated with GPR55, which means that the effects of endocannabinoids depend on the status of other cellular components, in this case the integrin binding proteins which allow the GPR55 activity. It is extremely important to deepen into the mechanisms reported by Waldeck-Weiermair *et al*. [41] in order to know their physiological implications.

Following this line of thought, the first proposal that this mini-review establishes is that GPR55 should be systematically considered when testing cannabinoids pharmacological effects. If so, we may prevent misinterpretations about the cannabinoids pharmacological profile under description and the receptors involved (*i.e.*, if CB_1, CB_2, GPR55 receptor heteromers or physical interactions). In supporting the above notion, at least two GPR55 selective antagonists are commercially available: CID16020046 [42] and ML-193 [43].

POTENTIAL EXPRESSION OF GPR55 IN THE CENTRAL NERVOUS SYSTEM

The GPR55 is a classical seven transmembrane-spanning domain which activates a G-protein Gαq/12 and Gα13, increasing the intracellular Ca2+, ERK phosphorylation, protein RhoA activation, among other nuclear effects [35]. GPR55 receptor was cloned in 1999 [44]; the gene that encodes this receptor is located in the chromosome 2q37, which deletion (the deletion of several genes included the involved in GPR55 synthesis) is associated with numerous consequences (not mentioned here) in development and behavior [45]. Human GPR55 mRNA was reported to be highly located in the putamen and caudate nucleus [44]. Fig. (**1**) shows a schematic representation of the relative potential expression of GPR55 in some areas in the rat brain (data taken from 1). In this study, levels of GPR55 mRNA were evaluated in different brain rat areas and normalized with the ribosomal protein m36B4 which levels are quite constant in the cell [46]. The brain areas with the higher levels of relative GPR55 mRNA expression found by Ryberg *et al*. [1] were the frontal cortex, striatum and hypothalamus. Similarly, Wu *et al*. [18] also evaluated the expression of GPR55 mRNA in some brain areas and confirmed a high expression in the striatum, cortex and hippocampus. Interestingly, the activity of all these brain areas is highly modulated by CB_1 receptors [47]. A recent study (in monkeys and rats) shows that striatal GPR55 and CB_1 receptors seems to form heteromers [7], but there is not yet a description of their function. In the spinal cord, this receptor

is highly expressed in large dorsal root ganglion neurons [11] which peripheral receptors convey information from muscle, joints and skin [48]. There is expression of GPR55 mRNA also in the brainstem [1], but its functions (if any) remain unknown.

In summary: GPR55 is potentially expressed in different areas of the central nervous system associated with several behaviors and physiological processes as learning and memory (striatum and hippocampus), emotions (the limbic system), metabolism (hypothalamus), sensory control and cognitive functions (frontal cortex), among others [1, 16, 18], but the description of its role in this processes is in the best of the cases incipient and remain to be comprehensively elucidated. In addition, mutant mice lacking GPR55 behave normally in several assays assessed by Wu *et al*. [11]. These findings must be taken into consideration to complement and validate all those findings regarding GPR55 expression, pharmacological agonists/antagonists and mutant mice assays. In addition, the use of more selective methods to stimulate GPR55 (*e.g*., optogenetics) will help to augment clarity about the specific function of GPR55 in the CNS.

NEURAL ACTIVITY OF GPR55

It is not clear if GPR55 is expressed pre-synaptically, post-synaptically or both. However, both the neuron as the glia seems to express functional GPR55 [1, 49]. In the periphery, this receptor is highly expressed post-junctionally in the neuro-effector cell (*i.e*., endothelial cells) [50]. In the central nervous system, GPR55 seems to potentiate the vesicular release of glutamate in hippocampal slices [19], suggesting a pre-synaptic expression. This effect may be explained by its capacity for increasing intracellular calcium and inhibiting potassium currents [11]. These data suggest GPR55 induces the opposite action of CB_1 receptor on the neural activity (which is predominantly inhibitory) [10]. The increase in intracellular calcium induced by GPR55 has been reported in both neural (periaqueductal gray cells) [51] and non-neural cells (endothelium) [52]. Nuclear signaling actions are integrated after GPR55 stimulation *via* RhoA proteins (which participate in the cytoskeleton dynamics) and extracellular signal-regulated kinase (ERK, which participate in proliferation, differentiation and several cellular processes) [53, 54]. Interestingly, the triggering of these signaling cascades depends on the agonist used for stimulating the GPR55; apparently, LPI fully activate every signaling cascade available while cannabinoids do it partially in mutant cells that over express GPR55 [53]. Obara *et al*. [4] by using PC12 cells *in vitro* that naturally express GPR55 (but not CB_1/CB_2) reported that LPI induced retraction of neurites. The above effect was not by anandamide or 2-AG [4], supporting the suggestion of LPI as the endogenous ligand [2].

GPR55 may be a crucial element during the neural development. For example: morphology and axon growth in retinal projections [55] and spinal cord [56] seem to be controlled *via* GPR55. The above suggests that GPR55 may be an important receptor for regulating neural development in certain tissues related with the sensory system. In the adult rat hippocampus, administration of GPR55 agonists induced a neuroprotective effect (microglia-dependent) after excitotoxic lesions [49], but the action mechanisms remain obscure. In this context, Pietr *et al*. [50] reported high expression of GPR55 mRNA in mouse microglia. Also, microglia activation with lysophosphatidylinositol induced a pro-inflammatory response in *in vitro* studies [57]. Hence, it is possible that under some conditions GPR55 activation promotes neuro-inflammation potentially resulting in a reduction of pain threshold [16].

GPR55 MEDIATING SENSORY INFORMATION

GPR55 seems to participate in the sensory neural development [56] of nociceptive projections. Interestingly, its expression in adult animals seems to be limited to the proprioceptive fibers [48]. Supporting the latter, it has been found that sensory fibers involved in trigeminal pain transmission and meningeal vascular control are refractory to anandamide effect mediated by GPR55 [27]. Thus, it is possible that GPR55 may be functionally involved in the proprioception rather than nociception under physiological conditions in adult animals. However, GPR55 has been widely related with inflammation, but this effect may be mediated directly on the immune cells where it seems to promote leukocytes migration and activation [58]. Supporting the latter, Staton *et al*. [16] reported that mechanical hyper-algesia is absent in mutant mice lacking GPR55 while these mice exhibit high levels of anti-inflammatory interleukins. This evidence suggests peripheral GPR55 participation in regulating pro-inflamatory cytokines.

Interestingly, injections of LPI (GPR55 endogenous agonist; Table **1**) into the periaqueductal gray induced a pronociceptive effect [51]. Paradoxically, palmitoylethanolamide (PEA), a GPR55 endogenous agonist (Table **1**), is currently used in clinical trials to treat chronic pain [59]. Its action mechanisms are still under study, but intrathecal injections of PEA decreased both formalin-induced pain and expression of pro-inflammatory interleukins in rat spinal cord [60]. Thus, the PEA pain-killing actions seem to be integrated at central level and may involve GPR55 activation. In this sense, Guida *et al*. [61] reported that alterations in transmission and proteomic of glutamatergic fibers of the medial prefrontal cortex accompanying peripheral nerve injury were restored after cortex microinjections of PEA. However, PEA interacts with several molecules in the body. The role of GPR55 on these therapeutic effects remains to be clarified. Another evidence of GPR55 involvement in sensory control is those findings in the monkey retina where this receptor seems to be involved in the facilitation of vision under low light conditions [62].

In summary, there is supporting evidence indicating GPR55 expression on different sensory nerves. Its role in CNS seems to be related with neurites development and transmission of proprioceptive information and integration of nociceptive information during inflammation.

POTENTIAL ROLE OF GPR55 IN EMOTION AND COGNITIVE FUNCTIONS

Perhaps cognition is the field with less information about the physiological functions of GPR55. However, some isolated reports suggest that this receptor may exert important

behavioral actions. For example: central stimulation of GPR55 (after intracerebroventricular injections) induced an anxiolytic-like effect that was not only prevented by GPR55 blockers, but they in turn induced anxiety [63]. Expression of GPR55 mRNA on structures related with anxiety as the hippocampus, cortex and limbic system has been reported [1]. In fact, the GPR55 expression increased in the frontal cortex of male and in the hippocampus of female rats after exposure to experimental early life stress [64]. Interestingly, in a rat model of autism induced by prenatal exposition to valproic acid, a decrease in the expression of GPR55 in the frontal cortex and hippocampus was reported [65]. This scarce information suggests that alterations in GPR55 expression may sub-serve some cognitive pathology as autism and anxiety. However, further investigation in this area is needed.

GPR55 in the dorsolateral striatum seems to participate in the formation of procedural memories. GPR55 receptors blockade in the dorsolateral striatum with CID16020046 (GPR55 antagonist; Table **1**) shifts the learning curve of rats in T-maze to the right, with no apparent motor alterations [17]. In addition, infusion of the endocannabinoid noladin-ether during CB_1 blockade seems to facilitate learning in this paradigm by GPR55 activation [17]. However, as motor coordination is also integrated in the dorsal striatum and mutant mice lacking GPR55 exhibit motor coordination impairments [18], the direct participation of GPR55 in procedural learning and memory must be thoroughly investigated. Interestingly, GPR55 is also present in ventral striatum; however, no information about its participation in reward is available.

GPR55 is also expressed in both the hippocampus and in the cerebellum. These systems are involved in cognition. At present, no studies have been directed to investigate the functions of GPR55 in those structures.

Another potential unexplored role of GPR55 is in the treatment of epilepsy. At this respect, the main non-psychoactive compound from marihuana, the cannabidiol (CBD) exerts anticonvulsant effects. This compound seems to be useful in the treatment of epilepsy [66]. Interestingly, one the several action mechanisms of cannabidiol is the blockade of GPR55 (Table **1**).

POTENTIAL ROLE OF GPR55 IN MOTOR COORDINATION

Wu *et al*. [18] evaluated different characteristics of the mutant mice GPR55 knockout. They found impairment in the motor coordination. In our lab, we have seen in preliminary experiments that bilateral infusions of CID16020046 (>10 nM) in the dorsolateral striatum impair the performance of Wistar rats in the Rotarod (unpublished data). However, GPR55 mRNA is also expressed in other brain areas related with motor actions as the cerebellum [1] and in sensory proprioceptive neurons [11]. Nevertheless, the exact location of GPR55 controlling motor actions remains unreported.

GPR55 IN METABOLISM

It has been suggested that GPR55 may have a role in energy balance [67, 68]. Centrally, GPR55 mRNA is located in the hypothalamus where its function in controlling food intake has not been specifically investigated. However, the mutant mice GPR55 KO had normal feeding behavior [69]. These mutant animals also developed augmented fat mass, insulin resistance [69], and also decreased physical activity. At the moment, no study has revealed the hypothalamic participation of GPR55 (or lack thereof) in behaviours associated with food intake and energy balance. On the other hand, the peripheral expression of GPR55 mRNA includes the pancreatic islets, insulin-secreting β-cell [70] and adipose tissue [71]. Pharmacological stimulation of GPR55 with cannabinoids increases plasma insulin levels [69] decreasing plasma glucose levels *in vivo* [72]. On the other hand, obesity seems to be associated with hyperactivity of the human GPR55/LPI system [71] and the endocannabinoids as anandamide and 2-AG [73]. GPR55 importantly regulates the metabolism of glucose and lipids at peripheral level, but there is a lack of information about its function (if any) in controlling feeding behavior in the CNS (*e.g*., the hypothalamus).

CONCERNS ABOUT OFF-TARGET EFFECTS INDUCED BY LYSOPHOSPHATIDYINOSITOL

Since Oka *et al*. [2, 3] reports, lysophosphatidylinositol is considered a GPR55 endogenous agonist. However, it is important to highlight the lack of selectivity of this lipid on GPR55. For example, Bodarenko *et al*. [52] reported that some lysophosphatidylinositol-induced depolarizing electrical responses in endothelial cell are mediated by non-selective cation channels (GPR55-independently). Moreover, Soga *et al*. [74] reported lysophophatidylinositol induction of insulin secretion in *in vitro* studies *via* GPR119. Other targets have also been studied, *i.e*. TRPV2 [75]. Therefore, it is advisable the use of selective GPR55 antagonists to evaluate the selectivity of any lysophosphatidylinositol-induced effect in order to avoid misleading interpretations.

FINAL CONSIDERATIONS

As we have shortly discussed, GPR55 is enormously related with multiple functions in the CNS. In almost every case, the lack of information is still an important issue. One limit that must be considered before suggesting a therapeutic GPR55-based treatment is its probed relationship with human tumors (where is highly expressed) which drives to proliferation and increase in tumor aggressiveness [76].

CONCLUSION

An everyday increasing literature supports the tight relationship between GPR55 and the endocannabinoid system. This receptor seems to function in several (although not very well understood) physiological and pathological processes. Increasing our knowledge about the physiology of this receptor will help us to understand the cellular control exerted by lipids in the brain.

LIST OF ABBREVIATIONS

2-AG = 2-araquidonylglicerol

CB_1 = cannabinoid receptor type 1

CB_2	=	cannabinoid receptor type 2
CB_3	=	cannabinoid receptor type 3
CNS	=	Central nervous system
ERK	=	extracellular signal-regulated kinase
GPR55	=	G protein-coupled receptor 55
LPI	=	lysophosphatidylinositol
NADA	=	N-araquidonyldopamine
PEA	=	palmitoylethanolamide
PPAR	=	peroxisome proliferator-activated receptors
TRPV1	=	transient receptor potential cation channel

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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