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Pharmacological characterization of GPR55, a putative cannabinoid receptor

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ABSTRACT

GPR55 has recently attracted much attention as another member of the cannabinoid family, potentially explaining physiological effects that are non-CB1/CB2 mediated. However, the data gathered so far are conflicting with respect to its pharmacology. We review the primary literature to date on GPR55, describing its discovery, structure, pharmacology and potential physiological functions. The CB1 receptor antagonist/inverse agonist AM251 has been shown to be a GPR55 agonist in all reports in which it was evaluated, as has the lysophospholipid, lysophosphatidylinositol (LPI). Whether GPR55 responds to the endocannabinoid ligands anandamide and 2-arachidonylglycerol and the phytocannabinoids, delta-9-tetrahydrocannabidiol and cannabidiol, is cell type and tissue-dependent. GPR55 has been shown to utilize G_q, G_{12}, or G_{13} for signal transduction; RhoA and phospholipase C are activated. Experiments with mice in which GPR55 has been inactivated reveal a role for this receptor in neuropathic and inflammatory pain as well as in bone physiology. Thus delineating the pharmacology of this receptor and the discovery of selective agonists and antagonists merits further study and could lead to new therapeutics.

Contents

1. Introduction

Marijuana remains the most widely used illegal drug (Murray et al., 2007), and its validated targets include plasma membrane cannabinoid receptors, many of which are found in the central nervous system. The diverse physiological effects produced by marijuana and cannabinoid ligands suggest the possibility that several receptors are responsible for their activity. Yet to date, only two receptor subtypes, CB1 and CB2, have convincingly been confirmed as cannabinoid targets. However, in support of the notion that other cannabinoid receptors remain to be identified, the complex pharmacological properties of exogenous cannabinoids and endocannabinoids are not fully explained by CB1 and CB2 signal transduction. Recently, the orphan G-protein coupled receptor, GPR55, was presented as one of the missing candidate cannabinoid receptor subtypes (Johns et al., 2007; Ryberg et al., 2007), but the validity of this assignment is under debate. In particular, Oka et al (2007) reported that while cannabinoids did not appear to activate GPR55, lysophosphatidyinositol (LPI) derivatives resulted in robust stimulation of the receptor. Thus, the chemical space of GPR55 agonists

Abbreviations: 2-AG, 2-arachidonylglycerol; 2-AGPI, 2-arachidonoyl-sn-glycero-3-phosphoinositol; (e-aR, anandamide endothelial receptor; abn-CBD, abnormal cannabidiol; βarr2-GFP, β-arrestin2-green fluorescent protein; CBD, cannabidiol; Δ^9-THC, delta-9-tetrahydrocannabidiol; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; LPI, lysophosphatidylinositol; PEA, palmitoylethanolamide PKCβII-GFP, Protein kinase C betall-green fluorescent protein; ROCK, Rho A-associated kinase.

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remains ill defined. As a consequence of the identification, whether correct or incorrect, that GPR55 is a target for cannabinoid binding, GPR55 now shoulders a potentially important but un-defined role in the paradigm of drug addiction. It thus becomes incumbent to identify GPR55-selective ligands in order to substantiate GPR55 pharmacology and to characterize its biology.

GPR55 was initially identified as a candidate cannabinoid receptor in patent applications from GlaxoSmithKline and AstraZeneca (Brown & Wise, 2001; Drmota et al., 2004). The ability of GPR55 to recognize cannabinoids was first described in a yeast expression system in the GlaxoSmithKline patent, where the CB1 antagonists AM251 and SR141716A acted as agonists at micromolar concentrations (Brown & Wise, 2001; Brown & Hiley, 2009) (please see Fig. 1 for structures). In contrast, the AstraZeneca group reported that when GPR55 was expressed in HEK293 cells, nanomolar concentrations of many cannabinoid agonists stimulated GTPγS binding (Drmota et al., 2004; Ryberg et al., 2007). Most of the endocannabinoids, including anandamide, 2-arachidonylglycerol (2-AG), virodhamine, noladin ether, oleoylethanolamide and palmitoylethanolamide as well as the several agonists including CP55,950 and Δ^9-THC, stimulated GTPγS binding, which was not antagonized by AM281, but was blocked with 450 nM cannabidiol (CBD) (Drmota et al., 2004; Ryberg et al., 2007). AM251 produced an agonist response in HEK293 cells, similar to that found in the yeast expression system (Ryberg et al., 2007). Lauckner et al (2008) reported that GPR55 was a cannabinoid receptor, based on their data that Δ^9-THC, anandamide and JWH-015, increased intracellular calcium in transfected cells and also in large dorsal root ganglion neurons. In contrast to these results, Oka et al (2007) reported that GPR55 is not a typical cannabinoid receptor as numerous endogenous and synthetic cannabinoids, including many mentioned above, had no effect on GPR55 activity. Instead, their data suggests that the endogenous lipid LPI and its 2-arachidonyl analogs are agonists at GPR55 as a result of their abilities to phosphorylate extracellular-regulated kinase and induce calcium signaling (Oka et al., 2007; Oka et al., 2009c). Thus GPR55 may recognize cannabinoids, but has a unique response profile differing from CB1 and CB2.

Several recent reviews have highlighted the enigmatic pharmacology of GPR55 (Brown & Hiley, 2009; De Petrocellis & Di Marzo, 2009; Godlewski et al., 2009; Kreitzer & Stella, 2009; Ross, 2009). Here we review the primary literature and include papers and abstracts not previously cited.

2. Discovery of GPR55

Human GPR55 (hGPR55) was originally isolated in 1999 as an orphan GPCR with high levels of expression in human striatum (Sawzdargo et al., 1999) (Genbank accession # NM_005683.3). Initial characterization of human GPR55 identified it as a potential member of the purinergic or chemokine receptor family based on amino acid homology; it shares 29% identity with the P2Y5 purinergic receptor (NM_005767.4), 30% identity with GPR23 (NM_005296.2), 27% identity with GPR35 (NM_005301.2) and 23% identity with the CCR4 chemokine receptor (NM_005508.4) (Sawzdargo et al., 1999). Relevant to later discussion, GPR23 has been classified as the LPAR4 receptor, although LPA activates at high micromolar concentrations

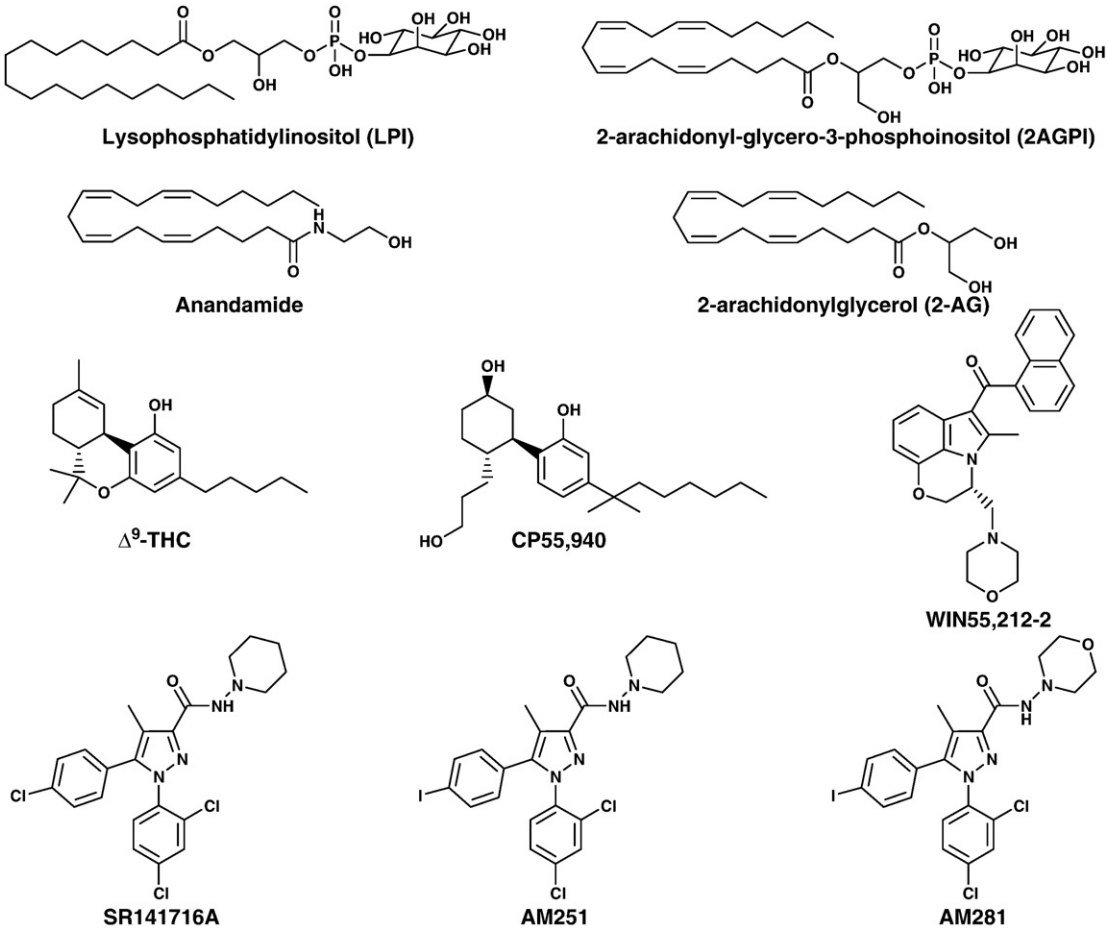

Fig. 1. The structures of several compounds studied as GPR55 ligands. Lysophosphatidylinositol (LPI) and 2-arachidonyl-glycero-3-phosphoinositol (2AGPI) are lysosphospholipid agonists of GPR55. Anandamide and 2-arachidonylglycerol (2-AG) are endocannabinoids. THC is a phytocannabinoid and CP55,940 the prototypical non-classic cannabinoid agonist. WIN55,212-2 is the prototypical aminoalkylindole compound. SR141716A, AM251 and AM281 are pyrazole CB1 receptor antagonists/inverse agonists.