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COMMENTARY

GPR55: a new member of the cannabinoid receptor clan?

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In this issue of the *British Journal of Pharmacology*, Ryberg *et al.* present convincing *in vitro* evidence that the orphan GPCR, GPR55, is a cannabinoid receptor. GPR55 was activated by a range of plant, synthetic and endogenous cannabinoids and blocked by the non-psychoactive phytocannabinoid, cannabidiol. Their experiments have revealed several differences between the pharmacology of GPR55 and the established cannabinoid CB_1 and CB_2 receptors. For example, the CB_1 receptor antagonist, AM251, activated GPR55 and the main psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol, displayed greater efficacy at GPR55 than at CB_1 or CB_2 receptors. They also compared the distribution of GPR55 and CB_1 mRNA in mouse and report that GPR55 couples to $G\alpha_{13}$, that it is activated by virodhamine, palmitoylethanolamide and oleoylethanolamide, and that virodhamine displays relatively high efficacy as a GPR55 agonist. Still to be identified are the main roles played by GPR55 in health and disease and any potential therapeutic benefits of activating or blocking this receptor.
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Keywords: GPR55; cannabinoid receptors; cannabis; Δ^9-tetrahydrocannabinol; cannabidiol; anandamide; 2-arachidonoylglycerol; AM251; virodhamine; palmitoylethanolamide

Abbreviations: Abnormal-cannabidiol, *trans*-4-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol; AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamideAM281, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; CP55940, (–)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol; GTPγS, guanosine-5′-*O*-(3-thiotriphosphate); HU-210, (6a*R*)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol; noladin ether, 2-arachidonylglyceryl ether; O-1602, *trans*-4-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-methyl-1,3-benzenediol; SR141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride; THC, tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid-1 receptor; virodhamine, *O*-arachidonoylethanolamine; WIN55212-2, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone

A major milestone in the field of cannabinoid pharmacology was the discovery that many effects of Δ^9-THC, the main psychoactive constituent of cannabis, are mediated by receptors, two types of which have so far been identified. These are the CB_1 and CB_2 receptors, which both signal through $G_{i/o}$ protein (reviewed in Howlett *et al.*, 2002; Pertwee, 2005a, 2006). A second equally momentous discovery was that mammalian tissues can synthesize and release compounds that activate cannabinoid receptors, the first of these 'endocannabinoids' to be identified being *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (Devane *et al.*, 1992; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995). Together with their receptors, these and other more recently discovered endocannabinoids (reviewed in Pertwee, 2005b) form a part of the 'endocannabinoid system'.

There is growing evidence that some but not all ligands for CB_1 and/or CB_2 receptors target additional receptors, either established or putative (reviewed in Pertwee, 2004, 2005a). One such receptor that has been attracting particular interest among cannabinoid scientists in recent times is the orphan receptor, GPR55. This interest was initially prompted by patents lodged by GlaxoSmithKline (Brown and Wise, 2001) and AstraZenica (Drmota *et al.*, 2004), which claim that this receptor is activated by several CB_1/CB_2 receptor ligands, and was further fuelled by two presentations made at the 2005 meeting of the International Cannabinoid Research Society by scientists from each of these pharmaceutical companies (Brown *et al.*, 2005; Sjögren *et al.*, 2005) and by a review article based mainly on these presentations and on the GPR55 patents (Baker *et al.*, 2006). Frustratingly, however,

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there was a total absence of any peer-reviewed data supporting the claim that GPR55 is a cannabinoid receptor. Happily, this need has now been met by Ryberg *et al*. (2007) in this issue of the *BJP*.

In their paper, Ryberg *et al*. (2007) describe the cloning and protein sequences of human, mouse and rat GPR55 and report that the CB_1/CB_2 receptor ligand, [^{3}H]CP55940, exhibits specific binding to human GPR55. Furthermore, they present evidence that this receptor can be activated by the established CB_1/CB_2 receptor agonists, Δ^9-THC, HU-210, CP55940, anandamide and 2-arachidonoylglycerol, and by the CB_1-selective agonist noladin ether. These agonists were all found to share the ability to stimulate [^{35}S]GTPγS binding to GPR55 with EC_{50} values in the low nanomolar range (Table 1) and E_{max} values ranging from 73 to 100%. The finding that anandamide and 2-arachidonoylglycerol activated GPR55 raises the possibility that these compounds may serve as endogenous agonists not only for CB_1 and CB_2 receptors but also for GPR55. Also described is the heterogeneous distribution pattern in mouse of GPR55 mRNA, the levels of which were the highest in adrenal tissue, ileum, jejunum, frontal cortex and striatum. Mouse brain contained less GPR55 mRNA than CB_1 mRNA in many of the areas investigated, and this difference is most apparent in cerebellum and hippocampus.

Several pharmacological differences between GPR55 and CB_1 or CB_2 receptors are reported by Ryberg *et al*. (2007) (see Table 1). Particularly notable are their findings that the endocannabinoid, 2-arachidonoylglycerol, displays more than 170 times greater potency as an agonist at GPR55 than at the CB_1 or CB_2 receptor and that Δ^9-THC has greater efficacy (though not greater potency) as an agonist for GPR55 ($E_{max} = 92\%$) than for CB_1 or CB_2 receptors ($E_{max} = 61$ and 67% respectively). Also noteworthy are their findings that GPR55 couples to $G_{\alpha 13}$ and not to $G_{i/o}$ or G_q, that this receptor is activated by AM251 at concentrations at which it behaves as an antagonist/inverse agonist at the CB_1 receptor (reviewed in Pertwee, 2005a), that CP55940 is 25 times and HU-210 is 130 times less potent at activating GPR55 than at activating CB_1 receptors, that CP55940-induced activation of GPR55 is antagonized by cannabidiol with an IC_{50} (445 nM) that is below any concentration at which this plant cannabinoid displaces [^{3}H]CP55940 from CB_1 or CB_2 receptors (Thomas *et al*., 2007) that GPR55 is neither activated nor antagonized by the CB_1/CB_2 agonist WIN55212-2 or by the CB_1-selective antagonist/inverse agonist, AM281, and that [^{3}H]WIN55212-2 lacks significant GPR55 affinity. Ryberg *et al*. (2007) also report that GPR55 is activated by the endogenous ligands, palmitoylethanolamide and oleoylethanolamide, which as expected, were found to lack significant activity as CB_1 or CB_2 receptor agonists in their experiments. Similarly, virodhamine displayed markedly greater potency as a GPR55 agonist than as a CB_1 or CB_2 agonist and, in addition, was found to exhibit particularly high efficacy at GPR55 ($E_{max} = 160\%$). They also found GPR55 to be activated in the [^{35}S]GTPγS-binding assay by O-1602 and abnormal cannabidiol. Neither of these compounds display detectable activity as a CB_1 or CB_2 agonist (Table 1), though both have been reported previously to target the putative abnormal-cannabidiol receptor, as has cannabidiol (reviewed in Pertwee, 2004, 2005a).

The findings reported by Ryberg *et al*. (2007) raise a number of important questions. First, to what extent are the pharmacological profiles of some CB_1 or CB_2 receptor agonists and antagonists shaped by their apparent ability to also activate GPR55? This is a question that will be particularly important to answer for AM251, because it is widely used as a research tool with which to block CB_1 receptors, for 2-arachidonoylglycerol because of the greater potency this endocannabinoid exhibited at GPR55 than at CB_1 or CB_2 receptors (Table 1), and for the psychoactive plant cannabinoid, Δ^9-THC, because of the greater efficacy it displayed at GPR55 than at CB_1 or CB_2 receptors (see above). Second, does rimonabant (SR141716A), which is now a licensed medicine (Acomplia, Sanofi-Aventis, Paris, France), a CB_1 receptor antagonist/inverse agonist (reviewed in

Table 1 EC_{50} values of GPR55 agonists for stimulation of [^{35}S]GTPγS binding to membranes obtained from cultured cells transfected with human GPR55, CB_1 or CB_2 receptors (from Ryberg *et al*., 2007)

GPR55 agonist		*EC_{50} (nM)*		
		GPR55	*CB_1*	*CB_2*
GPR55-selective	2-Arachidonoylglycerol	3	519	618
	palmitoylethanolamide	4	> 30 000	19 800
	virodhamine[a]	12	2920	381
	O-1602	13	> 30 000	> 30 000
	oleoylethanolamide	440	> 30 000	> 30 000
	abnormal-cannabidiol	2523	> 30 000	> 30 000
CB_1- and CB_2-selective	CP55940	5	0.2	0.3
	HU-210	26	0.2	0.5
	WIN55212-2	> 30 000	18	1
Other	Δ^9-Tetrahydrocannabinol[b]	8	6	0.4
	noladin ether	10	37	> 30 000
	anandamide	18	31	27
	AM251	39	Antagonist[c]	Antagonist[c]

Cannabidiol behaved as a GPR55 receptor antagonist.
[a]Virodhamine displayed the highest GPR55 efficacy.
[b]Δ^9-Tetrahydrocannabinol displayed higher efficacy at GPR55 than at CB_1 or CB_2 receptors.
[c]AM251 is much more potent at blocking CB_1 receptors than CB_2 receptors (reviewed in Pertwee, 2005a).

Howlett *et al*., 2002) and a structural analogue of AM251 and AM281, activate GPR55 (as reported for AM251) or fail to target this receptor (as reported for AM281)? Third, anandamide and 2-arachidonoylglycerol were found to activate GPR55, but to what extent are GPR55-mediated effects modulated by these or other endogenous compounds when they are released *in vivo*? Also, what are these effects and which endogenous compounds contribute most to any such modulation? Fourth, what physiological and pathological processes are modulated by GPR55, in what cell types and neuronal subpopulations is it most highly expressed, and will the signs of cannabinoid-induced activation of GPR55 be detectable in mice from which CB_1 and/or CB_2 receptors have been genetically deleted? Above all, what is the role of GPR55 in health and disease? Does this include the regulation of vascular tone and immune-cell migration, as suggested by Ryberg *et al*. (2007), and will any important clinical applications be discovered for cannabinoids that behave as selective agonists or antagonists for this receptor or for compounds that modulate the tissue levels of any endogenously released GPR55 receptor ligands?

In conclusion, Ryberg *et al*. (2007) present convincing evidence that GPR55 is targeted by a number of cannabinoids and that, intriguingly, it is activated as potently and with greater efficacy than the CB_1 receptor by the main psychoactive constituent of cannabis (Δ^9-THC) and much more potently than CB_1 or CB_2 receptors by the endocannabinoid, 2-arachidonoylglycerol. Now, it will be important to characterize the pharmacology of GPR55 and its ligands more completely through both *in vitro* and *in vivo* research, not least so that a conclusive decision can finally be made on whether GPR55 should indeed be accepted as a new member of the cannabinoid receptor clan.

Conflict of interest

The author states no conflict of interest.

References

Baker D, Pryce G, Davies WL, Hiley CR (2006). *In silico* patent searching reveals a new cannabinoid receptor. *Trends Pharmacol Sci* **27**: 1–4.

Brown AJ, Ueno S, Suen K, Dowell SJ, Wise A (2005). Molecular identification of GPR55 as a third G protein-coupled receptor responsive to cannabinoid ligands. *Symposium on the Cannabinoids*. International Cannabinoid Research Society: Burlington, Vermont, USA, p 16.

Brown AJ, Wise A (2001). Identification of modulators of GPR55 activity. *Patent number*, WO/2001/086305, http://www.wipo.int/pctdb/en/wo.jsp?wo=2001086305.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G *et al*. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **258**: 1946–1949.

Drmota T, Greasley P, Groblewski T (2004). Screening assays for cannabinoid-ligand type modulators of GPR55. *Patent number*, WO/2004/074844, http://www.wipo.int/pctdb/en/wo.jsp?wo=2004074844.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA *et al*. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* **54**: 161–202.

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR *et al*. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* **50**: 83–90.

Pertwee RG (2004). Novel pharmacological targets for cannabinoids. *Curr Neuropharmacol* **2**: 9–29.

Pertwee RG (2005a). Pharmacological actions of cannabinoids. In: Pertwee RG (ed). *Cannabinoids*. *Handbook of Experimental Pharmacology*, Vol. 168 Springer-Verlag: Heidelberg, pp. 1–51.

Pertwee RG (2005b). The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids. *AAPS J* **7**: E625–E654.

Pertwee RG (2006). Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol* **147**: S163–S171.

Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson N-O, Leonova J *et al*. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* **152**: 1092–1101 (this issue).

Sjögren S, Ryberg E, Lindblom A, Larsson N, Åstrand A, Hjorth S *et al*. (2005). A new receptor for cannabinoid ligands. In: (eds) *Symposium on the Cannabinoids*. International Cannabinoid Research Society: Burlington, Vermont, USA, p 106.

Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K *et al*. (1995). 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* **215**: 89–97.

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB_1 and CB_2 receptor agonists *in vitro*. *Br J Pharmacol* **150**: 613–623.