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REVIEW

Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors

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Cannabinoids act at two classical cannabinoid receptors (CB_1 and CB_2), a 7TM orphan receptor and the transmitter-gated channel transient receptor potential vanilloid type-1 receptor. Recent evidence also points to cannabinoids acting at members of the nuclear receptor family, peroxisome proliferator-activated receptors (PPARs, with three subtypes α, β (δ) and γ), which regulate cell differentiation and lipid metabolism. Much evidence now suggests that endocannabinoids are natural activators of PPARα. Oleoylethanolamide regulates feeding and body weight, stimulates fat utilization and has neuroprotective effects mediated through activation of PPARα. Similarly, palmitoylethanolamide regulates feeding and lipid metabolism and has anti-inflammatory properties mediated by PPARα. Other endocannabinoids that activate PPARα include anandamide, virodhamine and noladin. Some (but not all) endocannabinoids also activate PPARγ; anandamide and 2-arachidonoylglycerol have anti-inflammatory properties mediated by PPARγ. Similarly, ajulemic acid, a structural analogue of a metabolite of Δ^9-tetrahydrocannabinol (THC), causes anti-inflammatory effects *in vivo* through PPARγ. THC also activates PPARγ, leading to a time-dependent vasorelaxation in isolated arteries. Other cannabinoids which activate PPARγ include *N*-arachidonoyl-dopamine, HU210, WIN55212-2 and CP55940. In contrast, little research has been carried out on the effects of cannabinoids at PPARδ. In this newly emerging area, a number of research questions remain unanswered; for example, why do cannabinoids activate some isoforms and not others? How much of the chronic effects of cannabinoids are through activation of nuclear receptors? And importantly, do cannabinoids confer the same neuro- and cardioprotective benefits as other PPARα and PPARγ agonists? This review will summarize the published literature implicating cannabinoid-mediated PPAR effects and discuss the implications thereof.
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Keywords: cannabinoid; endocannabinoid; nuclear receptor; peroxisome proliferator-activated receptor

Abbreviations: 2-AG, 2-arachidonoylglycerol; CB, cannabinoid; COX, cyclooxygenase; IL, interleukin; LOX, lipoxygenase; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PPARs, peroxisome proliferator-activated receptors; THC, Δ^9-tetrahydrocannabinol; TZD, thiazolidinedione

Introduction

Peroxisome proliferator-activated receptors (PPARs) belong to a family of nuclear receptors comprising three isoforms: α, δ and γ. PPARs heterodimerize with the retinoid X receptor, and bind to DNA sequences called PPAR response elements, which lead to the transcription of target genes upon ligand activation. Ligand binding to PPARs causes the recruitment of regulator proteins that bind to a third site on PPARs and these are thought to modulate transactivation. PPARs target genes that are primarily involved in the regulation of metabolism and energy homeostasis, cell differentiation and inflammation, and the extensive research on PPARs has been expertly reviewed elsewhere (Bishop-Bailey, 2000; Ferre, 2004; Glass, 2006; Stienstra *et al.*, 2007). In brief, PPARα is found in metabolically active tissues such as liver, heart and muscle, and is involved in the regulation of fatty acid catabolism and inflammatory processes (Stienstra *et al.*, 2007). Ligands of PPARα, such as the fibrates, are used clinically in the treatment of hyperdyslipidemia. There are three variants of PPARγ: PPARγ1 is ubiquitously expressed, PPARγ2 is found in adipose tissue and PPARγ3 is found in macrophages (Auboeuf *et al.*, 1997). PPARγ is involved in the regulation of adipocyte formation, insulin sensitivity and inflammation (Fievet *et al.*, 2006; Stienstra *et al.*, 2007). Ligands of PPARγ, such as the thiazolidinediones (TZDs), are used clinically in the treatment of type 2 diabetes to improve insulin sensitivity. PPARδ (also known as PPARβ) is ubiquitously expressed. The function of this receptor was largely unknown for many years, but recent evidence suggests that it is a powerful metabolic regulator (Barish *et al.*, 2006). All three PPAR isoforms are also expressed in the brain and peripheral nervous system (Moreno *et al.*, 2004; Cimini *et al.*, 2005).

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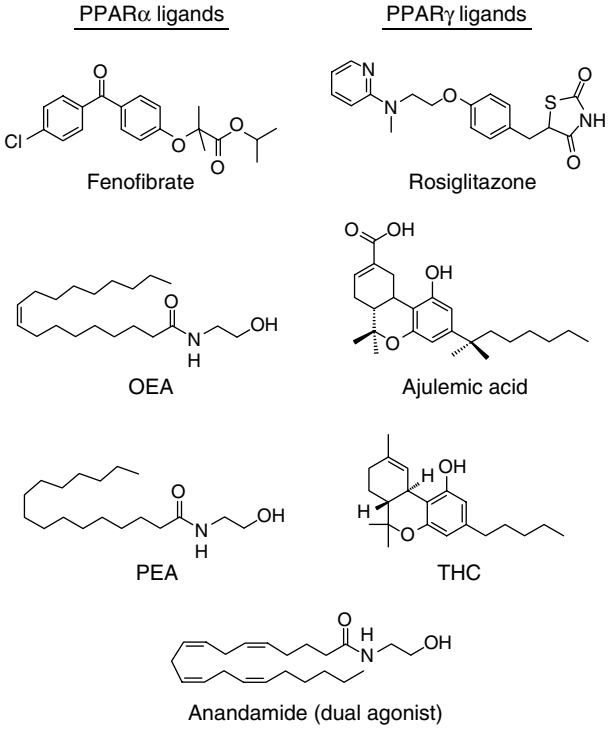

Figure 1 Chemical structure of known PPARα and PPARγ ligands, and of cannabinoids known to activate PPARs, including anandamide, which appears to be a dual agonist of both PPARα and PPARγ.

The ligand-binding domain of PPARs is unusually large, and consequently, they are relatively promiscuous, being activated by a number of natural and synthetic ligands of different chemical structure, including fatty acids and eicosanoids. The unsaturated fatty acids, linolenic acid, linoleic acid, petroselinic acid and arachidonic acid, are particularly good activators of PPARs, with EC_{50} values in the 2–20 μM range (Kliewer *et al*., 1997). The eicosanoids 15-deoxy-Δ-l2,14-prostaglandin J_2 and 8(S)-hydroxyeicosatetraenoic acid (8(S)-HETE) interact with PPARs with an EC_{50} of approximately 500 nM (Kliewer *et al*., 1997). By contrast, most synthetic ligands of PPARs have EC_{50} values in the low nanomolar range (Seimandi *et al*., 2005). It is of note that the chemical structures of clinically used PPAR ligands and those of cannabinoids vary greatly (see Figure 1).

The majority of cannabinoid ligand effects are thought to be mediated via cell surface receptors; there are two well-established seven-transmembrane (7TM) cannabinoid receptors (CB_1 and CB_2), with a further 7TM orphan receptor (GPR55) and the transmitter-gated channel transient receptor potential vanilloid type-1 receptor as additional sites of action. PPARs are sensors of fatty acid levels and, as endocannabinoids are fatty acid derivatives, it is not surprising that an increasing body of evidence now suggests that endocannabinoids activate PPARs, and this may mediate many of the biological effects of cannabinoids including anti-inflammatory actions, feeding behaviour and analgesia (see Table 1). This review will describe the literature implicating cannabinoid-mediated PPAR effects, discuss potential mechanisms of action, the future implications of this research and will highlight some outstanding research questions in this new area.

Cannabinoids and PPARα

The first evidence of cannabinoid interactions with PPARs came in 2002 in a study by Kozak *et al*., who showed that lipoxygenase (LOX) metabolism of the endocannabinoid, 2-arachidonoylglycerol (2-AG), produced a metabolite (15-hydroxyeicosatetraenoic acid glyceryl ester, 15-HETE-G, 1–10 μM) that increased the transcriptional activity of PPARα, as shown in a reporter gene assay. In 2003, it was then shown by Fu *et al*. that oleoylethanolamide (OEA, 0.1–10 μM) bound to and increased the transcriptional activity of PPARα, a finding later confirmed by Sun *et al*. (2006). OEA is a naturally occurring amide of ethanolamine and oleic acid, produced through biosynthetic pathways similar to those of anandamide but, despite the structural and metabolic similarities with anandamide, OEA does not bind to cannabinoid receptors. Fu *et al*. (2003) showed that the appetite-suppressing and weight-reducing effects of OEA (10 mg kg^{-1}) were absent in PPARα knockout mice, and that daily treatment with OEA (5 mg kg^{-1}, 2 weeks) reduced serum cholesterol levels in rat and mouse models of obesity. Guzman *et al*. (2004) then showed that the stimulatory effect of OEA (5 mg kg^{-1}, 4 weeks) on lipolysis *in vivo* was absent in PPARα knockout mice, and that a single dose of OEA (10 mg kg^{-1}) in rats increased the mRNA levels of a number of PPARα target genes (PPARα, fatty acid-binding protein and uncoupling protein 2). Further work has now shown that the anti-inflammatory effects of OEA in 12-*O*-tetradecanoylphorbol-13-acetate-induced oedema in mice (LoVerme *et al*., 2005) and the neuroprotective effects of OEA in a mouse model of cerebral artery occlusion (Sun *et al*., 2006) were also absent in PPARα knockout mice. Together, these studies suggest that many of the physiological responses to OEA are mediated by PPARα activation. A number of structural analogues of OEA have also been shown to have a high affinity for PPARα, with similar reductions in food intake when administered *in vivo* (Astarita *et al*., 2006).

Like OEA, another fatty acid ethanolamide, palmitoylethanolamide (PEA) is reported to have actions that cannot be attributed to traditional cannabinoid receptor sites of action. After demonstrating that OEA, which is structurally related to PEA, activates PPARα (Fu *et al*., 2003), Lo Verme *et al*. (2005) went on to show that PEA (1–30 μM) similarly activates PPARα transcriptional activity, causing anti-inflammatory actions in both 12-*O*-tetradecanoylphorbol-13-acetate-induced and carrageenan-induced oedema that were absent in PPARα knockout mice (at 10 mg kg^{-1}; LoVerme *et al*., 2006). Further studies showed that PEA (50 μg, intraplantar injection) caused analgesic effects *in vivo* in several models of pain behaviour, which were also absent in PPARα knockout mice (LoVerme *et al*., 2006). Other endocannabinoids shown to activate and bind to PPARα include anandamide, noladin ether and virodhamine (Sun *et al*., 2006), suggesting that PPARα activation is common to all endocannabinoids, or at least all those tested to date. It is of note that the concentrations of endocannabinoids

Table 1 Chronological review of some of the current evidence for cannabinoid/PPAR interactions.

Study	*Cannabinoid*	*PPAR*			*Method*	*Response*
		α	γ	δ		
Kozak *et al.* (2002)	2-AG	✓	x	x	Reporter gene assay	
Fu *et al.* (2003)	OEA	✓	x	✓	Reporter gene assay, direct binding and PPARα$^{-/-}$ mice	Appetite suppression and weight loss
Liu *et al.* (2003)	Ajulemic acid	x	✓	x	Binding and reporter gene assay adipogenesis	Anti-inflammatory
Guzman *et al.* (2004)	OEA	✓	—	—	PPARα$^{-/-}$ mice	Lipolysis
Rockwell and Kaminski (2004)	Anandamide	—	✓	—	PPARγ antagonist	Anti-inflammatory
LoVerme *et al.* (2006)	PEA	✓	x	x	Reporter gene assay and PPARα$^{-/-}$ mice	Anti-inflammatory
O'Sullivan *et al.* (2005)	THC	—	✓	—	Reporter gene assay, adipogenesis a PPARγ antagonist	Vasorelaxation
Bouaboula *et al.* (2005)	Anandamide	—	✓	—	Reporter gene assay, direct binding and adipogenesis	
Rockwell *et al.* (2006)	2-AG	—	✓	—	Reporter gene assay, adipogenesis PPARγ antagonist	Anti-inflammatory
LoVerme *et al.* (2006)	PEA	✓	—	—	PPARα$^{-/-}$ mice	Analgesia
Matias *et al.* (2006)	HU210	—	✓	—	Adipogenesis and PPARγ mRNA	
Sun *et al.* (2006)	WIN55212-2, OEA, anandamide, noladin ether and virodhamine	✓	—	—	Reporter gene assay and direct binding	Neuroprotection
Astarita *et al.* (2006)	OEA analogues	✓	—	—	Reporter gene assay	Anorexia

Abbreviations: 2-AG, 2-arachidonoylglycerol; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PPAR, peroxisome proliferator-activated receptor; THC, Δ^9-tetrahydrocannabinol.
✓, positive effect; x, no effect; —, no information available.

required to activate PPARs are in the same range as those reported for fatty acids (Kliewer *et al.*, 1997). However, it has not yet been established whether combinations of fatty acids/endocannabinoids (as would occur intracellularly) may act synergistically at PPARs.

The majority of research to date has focused on the effects of endocannabinoids on PPARα, and the effects of synthetic or phytocannabinoids at this receptor are yet to be investigated. The synthetic CB_1/CB_2 agonist, WIN55212-2, is reported to bind to and increase the transcriptional activity of PPARα (Sun *et al.*, 2006), although whether WIN55212-2 causes similar effects (anti-inflammatory actions, anorexia, lipolysis and analgesia) through this site, as reported for OEA and PEA, remains to be established.

Cannabinoids and PPARγ

In 2003, it was shown that the synthetic cannabinoid, ajulemic acid (an analogue of a tetrahydrocannabinol metabolite) binds to and increases the transcriptional activity of PPARγ in the concentration range of 1–50 μM (Liu *et al.*, 2003). It was also shown that ajulemic acid stimulates the differentiation of fibroblasts to adipocytes, which is a property of PPARγ ligands (Mueller *et al.*, 2002). The anti-inflammatory effects of ajulemic acid were suggested to be a result of PPARγ activation, since it was shown to inhibit the promoter activity of the proinflammatory cytokine, interleukin (IL)-8, in a PPARγ-dependent manner (Liu *et al.*, 2003).

Anandamide has anti-inflammatory effects, which are both cannabinoid receptor-dependent and -independent. Rockwell and Kaminski (2004) have shown that anandamide (10–20 μM) inhibited the secretion of the proinflammatory cytokine, IL-2, in a CB_1/CB_2 receptor-independent manner, which could be prevented by a PPARγ antagonist. In this study, the effects of anandamide were also reduced by a cyclooxygenase-2 (COX-2) inhibitor, although it was not clear whether the effects of anandamide were through activation of PPARγ directly, or via its metabolites. However, subsequent research has shown that anandamide binds directly to PPARγ (3–100 μM, Bouaboula *et al.*, 2005; Gasperi *et al.*, 2007), activates PPARγ transcriptional activity (3–30 μM) and stimulates the differentiation of fibroblasts to adipocytes (10 μM; Bouaboula *et al.*, 2005), so it is likely that anandamide is acting directly at PPARγ. 2-AG has been shown to bind to PPARγ with the same potency as anandamide (Bouaboula *et al.*, 2005), activate PPARγ transcriptional activity and stimulate the differentiation of fibroblasts to adipocytes (Rockwell *et al.*, 2006). As with anandamide, this was associated with inhibition of IL-2 secretion through the suppression of two proinflammatory transcription factors, which were sensitive to PPARγ antagonism (Rockwell *et al.*, 2006). An increase in the transcriptional activity of PPARγ is also stimulated by a third endocannabinoid, *N*-arachidonoyldopamine (1–20 μM; O'Sullivan *et al.*, 2006b). However,

PPARγ activation is not common to all endocannabinoids, as PEA does not increase the transcriptional activity of PPARγ (LoVerme *et al.*, 2006) or bind to PPARγ (Bouaboula *et al.*, 2005), and OEA does not increase the transcriptional activity of PPARγ (Fu *et al.*, 2003). The differential effects of endocannabinoids at PPARγ, as opposed to PPARα, where all endocannabinoids tested appear to be ligands, remain to be investigated.

The stimulation of adipogenesis is a property of PPARγ ligands (Mueller *et al.*, 2002). Interestingly, endocannabinoid levels are increased during adipocyte differentiation (Matias *et al.*, 2006), and cannabinoid receptor binding efficiency, CB_1 receptor expression and fatty acid amide hydrolase (FAAH) expression are all increased after adipocyte differentiation (Gasperi *et al.*, 2007). Whether these changes in protein levels are as a consequence of PPARγ activation remains to be determined, but it appears that PPARγ activation may affect the endocannabinoid system.

Our group has shown that the active ingredient of cannabis, Δ^9-tetrahydrocannabinol (THC, 100 nM–10 μM), activates the transcriptional activity of PPARγ, stimulates adipogenesis and causes time-dependent, PPARγ-dependent vasorelaxation in isolated blood vessels (O'Sullivan *et al.*, 2005). This response was dependent on nitric oxide (NO) and hydrogen peroxide (H_2O_2) production, and superoxide dismutase (SOD) activity (O'Sullivan *et al.*, 2005). Furthermore, subsequent studies showed that 2-h incubation with THC (10 μM) *in vitro* blunts subsequent contractile responses and enhances vasodilator responses in isolated arteries, which was also inhibited by a PPARγ antagonist (O'Sullivan *et al.*, 2006a). These experiments similarly indicated a role for increased SOD activity and H_2O_2 production stimulated by THC, and together these studies suggest that THC, through activation of PPARγ, leads to increased synthesis of SOD, promoting vasorelaxation by preventing NO being scavenged by endogenous superoxides and also catalyzing the conversion of superoxides to H_2O_2 (see Figure 2). This is in agreement with a recent study showing that, in addition to direct effects on NO production, PPARγ ligands enhance NO bioavailability in blood vessels through induction of SOD (Hwang *et al.*, 2005).

Other cannabinoids which activate the transcriptional activity of PPARγ, as measured in reporter gene assays, include WIN55212-2, CP55940 and cannabidiol (1–20 μM; O'Sullivan *et al.*, 2006b). The potent CB_1/CB_2 receptor agonist HU210 (100 nM) has been shown to induce adipogenesis and increase the mRNA of PPARγ within cells (Matias *et al.*, 2006), suggesting PPARγ activation (Mueller *et al.*, 2002).

Cannabinoids and PPARδ/β

PPARδ is the least investigated of the three PPAR isoforms, but has been proposed as a regulator of metabolic function (Barish *et al.*, 2006). There is currently little information on the effects of cannabinoids at this nuclear receptor. Fu *et al.* (2003) showed that OEA activates the transcriptional activity of PPARδ, but no further studies were carried out on the potential physiological consequences. Ajulemic acid

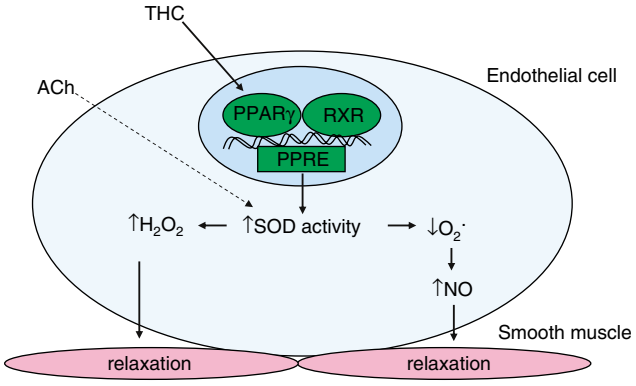

Figure 2 Mechanisms of time-dependent vasorelaxation to THC in isolated blood vessels. THC activates PPARγ within endothelial cells, leading to the transcription and translation of target proteins. One protein identified is superoxide dismutase (SOD), which can prevent NO being scavenged by endogenous superoxide anion, and also catalyses the conversion of superoxide to H_2O_2, both of which cause vasorelaxation of underlying smooth muscle (O'Sullivan *et al.*, 2005). Other PPARγ ligands (ciglitazone or 15d-PGJ_2) also enhance NO bioavailability through induction of SOD (Hwang *et al.*, 2005). Pre-incubation with THC also promotes agonist-stimulated vasorelaxation (to acetylcholine) by similar mechanisms (O'Sullivan *et al.*, 2006a, b). 15d-PGJ_2, 15-deoxy-Δ-12,14-prostaglandin J_2; H_2O_2, hydrogen peroxide; NO, nitric oxide; PPARs, peroxisome proliferator-activated receptors; THC, Δ^9-tetrahydrocannabinol.

(Liu *et al.*, 2003), 2-AG metabolites (Kozak *et al.*, 2002) and PEA (LoVerme *et al.*, 2006) have all been shown not to activate PPARδ. Despite this, there is some evidence to suggest that the endocannabinoid system and PPARδ may be linked. Yan *et al.* (2007) recently showed that silencing PPARδ by RNA interference significantly increased CB_1 receptor expression, and conversely that overexpression of PPARδ significantly reduced CB_1 receptor expression, although the physiological relevance of this is unclear.

Mechanism of action: binding, metabolism or indirect actions?

Many studies have shown that cannabinoids activate the transcriptional activity of PPARs, have responses that are inhibited by PPAR antagonists or have responses that are absent in PPAR gene-disrupted animals. However, it is still unclear as to the exact mechanisms by which cannabinoids interact with PPARs. As shown in Figure 3, there are several potential mechanisms by which cannabinoids can activate PPARs; direct binding, metabolism to other compounds that directly bind to PPARs or via intracellular signalling. The possibility also exists that some cannabinoids may activate PPARs both directly and indirectly.

Direct binding of cannabinoids to PPARs has been demonstrated in several studies, including OEA (Fu *et al.*, 2003; Sun *et al.*, 2006), ajulemic acid (Liu *et al.*, 2003), anandamide (Bouaboula *et al.*, 2005; Gasperi *et al.*, 2007), WIN55212-2, noladin ether and virodhamine (Sun *et al.*, 2006). Recent crystallography studies using ajulemic acid suggest that this compound occupies approximately 30% of the ligand-binding cavity of PPARγ and forms polar contacts

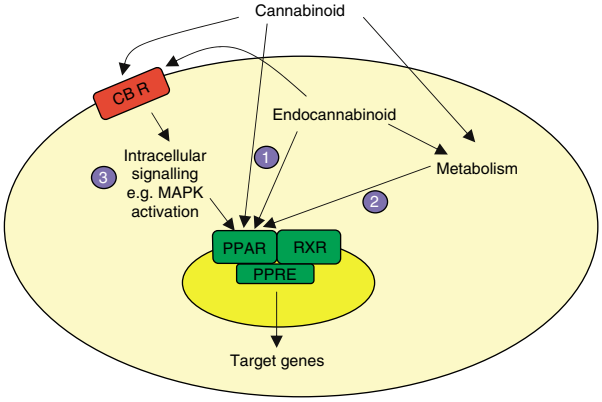

Figure 3 Potential mechanisms of cannabinoid/PPAR interactions. (1) Some studies have shown that cannabinoids and endocannabinoids directly bind to PPARs to bring about changes in target gene expression. (2) Some studies have implicated that it is the conversion of cannabinoids into metabolites, which are active at PPARs. (3) A third possibility is that cannabinoids, acting at cell surface receptors, may initiate intracellular signalling cascades that lead to the activation of PPARs. Potentially, all three pathways contribute to the effects of cannabinoid at PPARs, and the relative contributions of each pathway may be different between cells and tissues depending on the expression of various receptors and enzymes within that cell. PPARs, peroxisome proliferator-activated receptors.

mainly with the ω-loop, and not the C-terminal helix H12, as it has been observed for other ligands (Ambrosio *et al.*, 2007), and this may explain why cannabinoids, such as ajulemic acid, are less potent than synthetic ligands. Ajulemic acid also appears to bind to the co-regulator site of PPARγ (Ambrosio *et al.*, 2007), but it has not been investigated whether other cannabinoids bind to this site. Further crystallography studies are also required to address the question as to why cannabinoids act differentially at the various PPAR isoforms.

Some studies have implied that it is the metabolites of cannabinoids that are the active ligands at PPARs. Rockwell and Kaminski (2004) showed that suppression of IL-2 secretion by anandamide is inhibited both by COX-2 inhibition and PPARγ antagonism, and suggest that COX-2 metabolites of anandamide may be responsible for PPARγ activation by anandamide. Kozak *et al.* (2002) also showed that LOX metabolism of 2-AG produces a metabolite, 15-HETE-G, which is active at PPARα. Breakdown of endocannabinoids through various pathways to biologically active metabolites leads to a number of molecules that may interact with PPARs such as fatty acids, ethanolamine and various COX-2 and LOX metabolites, although it remains to be established whether this is true of all endocannabinoids, and which metabolites are PPAR activators.

A third possibility is that cannabinoids activate cannabinoid receptors at the cell surface, initiating intracellular signalling that may lead to PPAR activation. For example, in macrophages, statins activate PPARs through activation of extracellular signal-regulated kinase-1/2 and p38 mitogen-activated protein kinase pathways (Yano *et al.*, 2007). Both of these pathways can also be activated by cannabinoid receptor activation (Rubino *et al.*, 2005; Upham *et al.*, 2003; Demuth and Molleman, 2006), and therefore represent a third mechanism by which cannabinoids may activate PPARs as a result of cannabinoid receptor activation (see Figure 2).

Implications

Given the established beneficial effects of PPAR ligands in a variety of diseases, such as type 2 diabetes, cancer, hyperlipidemia, atherosclerosis, metabolic syndrome and neurodegenerative disorders (for reviews see Francis *et al.*, 2003; Fenner and Elstner, 2005; Barish *et al.*, 2006; Glass, 2006; Leo *et al.*, 2007; Stienstra *et al.*, 2007), cannabinoid actions at PPARs would provide an alternative mechanism of action for cannabinoids as therapeutic agents. Cannabinoids also represent an alternative group of structurally novel PPAR agonists. For example, the TZDs are a group of PPARγ agonists that are used in the management of type 2 diabetes to improve insulin sensitivity through activation of PPARγ (for reviews see Ferre, 2004; Rangwala and Lazar, 2004). However, it is generally recognized that there are several side effects associated with TZDs, including weight gain, oedema and increased plasma lipoproteins (Gelman *et al.*, 2007). New PPARγ agonists that do not possess these side effects are being investigated, and it is suggested that partial or weak agonists may be beneficial for low-level PPARγ activation (Gelman *et al.*, 2007). Cannabinoids (endogenous, phyto-derived and synthetic) do not bind to or activate PPARs to the same extent as currently available synthetic ligands such as the TZDs (Seimandi *et al.*, 2005) and may therefore prove successful as weak agonists of PPARs. It is also worth noting that in 2004, the Food and Drug Administration (FDA) ruled that 2-year carcinogenicity studies in rodents must be completed before beginning clinical trials longer than 6 months in duration with PPAR agonists (FDA web site, 2004). Again, studies with partial agonists suggest there may be a way of developing agents that have the desired efficacy of PPAR agonists, without their potential carcinogenic effects.

Dual PPARα/PPARγ agonists, such as the glitazars, combine the triglyceride and cholesterol-lowering effects of PPARα agonists with the insulin sensitivity improving effects of PPARγ agonists, making them therapeutically attractive. Anandamide appears to activate both PPARα (Sun *et al.*, 2006) and PPARγ (Bouaboula *et al.*, 2005; Gasperi *et al.*, 2007); therefore, modulation of anandamide levels through inhibition of the enzyme that breaks it down may lead to activation of both PPARα and PPARγ. Similarly, WIN55212-2 has actions at PPARα (Sun *et al.*, 2006) and PPARγ (O'Sullivan *et al.*, 2006b), and could be administered exogenously for dual-receptor agonism. OEA is an agonist of PPARα and PPARδ (Fu *et al.*, 2003), and this combination may prove an interesting alternative therapy in the treatment of metabolic syndrome. Exploration of the potential pan-activation of PPARs by cannabinoids and their physiological effects may lead to the discovery of successful dual/pan agonists.

Recent evidence suggests that combining cannabinoids with other compounds (including other cannabinoids or PPAR agonists) may increase their therapeutic potential. For example, the combination of OEA, as a PPARα agonist, with rimonabant, a CB_1 receptor antagonist used for the treatment of obesity, is more effective in suppressing feeding and

increasing weight loss than either OEA or rimonabant alone in obese and non-obese rats (Serrano *et al.*, 2007). It is of note that our group has demonstrated that rimonabant can activate PPARγ (Randall *et al.*, 2007), and so the beneficial effects of combined rimonabant and OEA treatment could in fact represent a combination of CB_1 receptor antagonism with dual PPARα and PPARγ activation. A combination of anandamide, acting through the CB_1 receptor, and the PPARα agonist GW7647 has also been shown to have synergistic effects on reducing pain behaviour in the mouse formalin model (Russo *et al.*, 2007), although some benefits may also be derived from anandamide-induced PPARγ activation.

Much done, more to do!

In this newly emerging research area, there are still a number of research questions that remain to be answered. Why do cannabinoids act at some PPAR isoforms and not others? How many of the chronic effects of cannabinoids are mediated through activation of nuclear receptors? Given the numbers of orphan nuclear receptors remaining, are any of these activated by cannabinoids? Some PPAR ligands are known to act at orphan nuclear receptors, such as the retinoic acid receptor-related orphan receptor-α, and this might suggest that cannabinoids would similarly act at these sites. Does modulation of the endocannabinoid system lead to PPAR-mediated effects? Evidence suggests that PPAR activation affects CB_1 receptor expression, so does PPAR activation modulate other components of the endocannabinoid system? And as a consequence, do patients on long-term PPAR agonist pharmacotherapy (for example, gemfibrozil or rosiglitazone) have altered levels of endocannabinoids? Or, do patients with the conditions for which PPAR ligands are currently indicated (dyslipidemia and non-insulin-dependent diabetes mellitus) exhibit alterations in their endocannabinoid profiles? Many patients are already taking cannabis-based medicines such as Sativex; are these patients also receiving the benefits of chronic PPARγ activation? Continued research in this area will hopefully lead to exciting findings and may change the way we think about the effects of chronic cannabinoid use, administration and medicinal potential.

Summary

To summarize, research in the last 4 years has shown that cannabinoids, in particular endocannabinoids, are activators of the PPAR family of nuclear receptors. Studies have shown that the physiological responses to endocannabinoids such as PEA and OEA, previously shown not to be through the traditional cannabinoid receptors, are through activation of PPARs. These responses include regulation of feeding, weight loss, lipolysis, analgesia and anti-inflammatory effects. Continued investigation in the area is required to establish whether similar physiological responses mediated by PPARs can be brought about by phytocannabinoids and synthetic cannabinoids, and whether cannabinoids will confer the same neuro- and cardio-protective benefits as other PPAR agonists.

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Conflict of interest

The author states no conflict of interest.

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