

REVIEW ARTICLE

An update on PPAR activation by cannabinoids

Correspondence Saoirse Elizabeth O'Sullivan, School of Medicine, Royal Derby Hospital, University of Nottingham, Nottingham, DE22 3DT, UK. E-mail: saoirse.osullivan@nottingham.ac.uk

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Saoirse Elizabeth O'Sullivan

School of Medicine, Royal Derby Hospital, University of Nottingham

Some cannabinoids activate the different isoforms of PPARs (α , β and γ), as shown through the use of reporter gene assays, binding studies, selective antagonists and knockout studies. Activation of all isoforms, but primarily PPAR α and γ , mediates some (but not all) of the analgesic, neuroprotective, neuronal function modulation, anti-inflammatory, metabolic, anti-tumour, gastrointestinal and cardiovascular effects of some cannabinoids, often in conjunction with activation of the more traditional target sites of action such as the cannabinoid CB₁ and CB₂ receptors and the TRPV1 ion channel. PPARs also mediate some of the effects of inhibitors of endocannabinoid degradation or transport. Cannabinoids may be chaperoned to the PPARs by fatty acid binding proteins. The aims of this review are to update the evidence supporting PPAR activation by cannabinoids and to review the physiological responses to cannabinoids that are mediated, and not mediated, by PPAR activation.

Abbreviations

2-AG, 2-arachidonoyl-glycerol; AJA, ajulemic acid; CBD, cannabidiol; FAAH, fatty acid amide hydrolase; FABP, fatty acid binding protein; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; THC, Δ^9 -tetrahydrocannabinol; VCAM, vascular cell adhesion molecule

Tables of Links

TARGETS
GPCRs^a
CB ₁ receptor
CB ₂ receptor
GPR55
Nuclear hormone receptors^b
PPAR α
PPAR γ
Other proteins^c
FABP5, fatty acid binding protein 5
Enzymes^d
COX2
FAAH, fatty acid amide hydrolase

LIGANDS	
15d-PGJ ₂ , 15-deoxy- $\Delta^{12,14}$ -PGJ ₂	JWH015
2-AG, 2-arachidonoyl-glycerol	Methanandamide
Anandamide	OEA, oleoylethanolamide
Arachidonyl-2'-chloroethylamide	Oleamide
NADA, N-arachidonoyl-dopamine	PEA, palmitoylethanolamide
CBD, cannabidiol	THC, Δ^9 -tetrahydrocannabinol
CP55940	URB597
ICAM	VCAM, vascular cell adhesion molecule
IL-2	Virodhamine
IL-8, CXCL8	WIN55,212-2

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (^{a,b,c,d}Alexander *et al.*, 2015a,b,c,d).

Introduction

The PPARs are a family of nuclear hormone receptors with three isoforms (α , δ and γ , Alexander *et al.*, 2015b). PPARs form heterodimers with the retinoid X receptor and bind to DNA sequences called PPAR response elements, leading to changes in the transcription of target genes. Ligand binding to PPARs is associated with a change in the variety of regulator proteins that bind to a third site on PPARs, and these are thought to modulate transactivation. The target genes of PPARs are involved in the regulation of metabolism and energy homeostasis, cell differentiation and inflammation (see Friedland *et al.*, 2012; Menendez-Gutierrez *et al.*, 2012; Neher *et al.*, 2012; Poulsen *et al.*, 2012, for reviews).

PPARs have large ligand binding domains and can be activated by a number of ligands of different chemical structure, including a number of plant extracts (Wang *et al.*, 2014). Endogenous activators of PPARs include the unsaturated fatty acids linolenic acid, linoleic acid, petroselinic acid and arachidonic acid, with EC₅₀ values in the 2–20 μ M range (Kliwer *et al.*, 1997). Eicosanoids such as 15-deoxy- $\Delta^{12,14}$ -PGJ₂ (15d-PGJ₂) and 8S-HETE also interact with PPARs, with pEC₅₀ values of about 6.3 (Kliwer *et al.*, 1997). Clinically, PPAR α agonists are used in the treatment of cholesterol disorders and for their effects on triglyceride metabolism (fibrate drugs, Katsiki *et al.*, 2013), and PPAR γ agonists are used in the treatment of insulin resistance and decrease blood glucose levels (thiazolidinediones; Cariou *et al.*, 2012).

Since 2002, evidence has accumulated that endocannabinoids, endocannabinoid-like compounds, phytocannabinoids and synthetic cannabinoid ligands bind to and activate PPARs (O'Sullivan, 2007; O'Sullivan, 2013). This link has been identified through reporter gene assays, binding studies, the use of selective antagonists, knockout animals and siRNA knockdown studies, and these data are summarized in Tables 1 and 2. Because of this, investigators are increasingly assessing potential roles for PPAR activation as the basis of the physiological effects of cannabinoids. This means that a clearer picture of the relevance of PPAR activation by some cannabinoids is now emerging. The aims of this review are to update the evidence for cannabinoids as agonists of PPARs and to review the effects of cannabinoids that might be mediated through PPARs. I will also review the effects of cannabinoids that have been shown to be PPAR independent.

Evidence of PPAR activation by cannabinoids

A summary of the current data supporting the activation of PPAR nuclear receptors by some cannabinoid compounds and their derivatives is provided in Table 1 for PPAR α and Table 2 for PPAR γ . These Tables do not include those studies where a role for endocannabinoid activation of PPARs has been proposed after administration of fatty acid amide hydrolase (FAAH) inhibitors (Jhaveri *et al.*, 2008; Sagar *et al.*, 2008; Mazzola *et al.*, 2009; Luchicchi *et al.*, 2010; Khasabova *et al.*, 2012; Sasso *et al.*, 2013; Justinova *et al.*, 2015; Rock *et al.*, 2015), monoacylglycerol lipase inhibitors (Zhang *et al.*, 2014), *N*-acylethanolamine acid amidase inhibitors (Khasabova *et al.*, 2012; Sasso *et al.*, 2013), endocannabinoid uptake inhibitors (Roche *et al.*, 2008; Loria

et al., 2010; Reyes-Cabello *et al.*, 2012) or fatty acid binding proteins (FABP) inhibitors (Kaczocha *et al.*, 2014), and where the activating ligand was not specifically identified, but a role for PPAR activation was implied when endocannabinoid tone was increased.

Phytocannabinoids and their derivatives

Phytocannabinoids and their derivatives including Δ^9 -tetrahydrocannabinol (THC), cannabidiol (CBD), abnormal CBD, cannabigerol, cannabigerol quinone, cannabichrome and ajulemic acid (a synthetic analogue of a tetrahydrocannabinol metabolite, AJA) can all bind to, increase the transcriptional activity of and exert effects that are inhibited by selective antagonists of PPAR γ (see Table 2 for references), suggesting that this is a property of many phytocannabinoid compounds. However, tetrahydrocannabivarin does not increase the transcriptional activity of PPAR γ (O'Sullivan *et al.*, 2006). By contrast, there are less data on the effects of phytocannabinoids at PPAR α . Sun *et al.* (2007) found that THC does not bind to PPAR α , but Takeda *et al.* (2014) recently showed that THC did increase the transcriptional activity of PPAR α . AJA also does not bind to PPAR α or δ (Liu *et al.*, 2003).

Endocannabinoids and their derivatives

Strong evidence now exists that the endocannabinoid-like compounds oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) activate PPAR α , as shown through binding studies, reporter gene assays, the use of antagonists and also the absence of responses to these compounds in PPAR α knockout mice (see Table 1 for references). Anandamide, 2-arachidonoyl-glycerol (2-AG), noladin ether, virodhamine and oleamide have also been shown to activate PPAR α , although there is less evidence for this (Table 1). Several studies have shown that anandamide and 2-AG also activate PPAR γ (Table 1), and although less investigated, there is evidence that *N*-arachidonoyl-dopamine, PEA and oleamide also activate PPAR γ , although studies are contradictory in this area. In addition, studies have shown that some of the metabolites of endocannabinoid degradation are PPAR activators. Raman *et al.* (2011) showed that 2-AG-derived 15d-PGJ₂-glycerol ester activates PPAR γ in a reporter gene assay, and Kozak *et al.* (2002) showed that 2-AG-derived 15-hydroxyeicosatetraenoic acid glyceryl ester increases the transcriptional activity of PPAR α . Arachidonic acid derived from anandamide also activates PPAR δ (Yu *et al.*, 2014). Fu *et al.* (2003) also showed that OEA activates the transcriptional activity of PPAR δ , Dionisi *et al.* (2012) showed that oleamide increases the transcriptional activity of and binds to PPAR δ , Paterniti *et al.* (2013) showed that the neuroprotective and anti-inflammatory effects of PEA were inhibited by a PPAR δ antagonist, and an indirect activation of PPAR δ by anandamide (being degraded into arachidonic acid) is speculated to play a role in regulating cognitive function (Yu *et al.*, 2014). However, 2-AG metabolites (Kozak *et al.*, 2002) and PEA (LoVerme *et al.*, 2005) do not activate PPAR δ . Together, this suggests that activation of PPARs by endocannabinoids, endocannabinoid-like molecules and some of their metabolites is a common feature of these compounds.

Synthetic cannabinoids

Fewer studies have investigated the potential for synthetic cannabinoid compounds to activate PPARs. WIN55,212-2 binds

Table 1Current evidence for cannabinoid activation of PPAR α

	Binding studies	Transcriptional activity	Blockade by selective antagonists	Use of knockouts/siRNA
Phytocannabinoids and their derivatives				
THC	^a	Takeda <i>et al.</i> , 2014	Fishbein-Kaminietsky <i>et al.</i> , 2014	–
CBD	–	–	–	–
AJA	^a	^a	–	–
Endocannabinoids and endocannabinoid-like compounds				
AEA	Sun <i>et al.</i> , 2007	Sun <i>et al.</i> , 2007	Romano and Lograno, 2012	–
2-AG	–	Kozak <i>et al.</i> , 2002	–	–
Endocannabinoid-like compounds				
OEA	Fu <i>et al.</i> , 2003; Sun <i>et al.</i> , 2007	Fu <i>et al.</i> , 2003; Sun <i>et al.</i> , 2007; Kaczocha <i>et al.</i> , 2012	Melis <i>et al.</i> , 2008; Zhou <i>et al.</i> , 2012; Hind <i>et al.</i> , 2015	Fu <i>et al.</i> , 2003; Guzman <i>et al.</i> , 2004; Sun <i>et al.</i> , 2007; Campolongo <i>et al.</i> , 2009; Gaetani <i>et al.</i> , 2010; Bilbao <i>et al.</i> , 2013
PEA	–	LoVerme <i>et al.</i> , 2005	Melis <i>et al.</i> , 2008; Koch <i>et al.</i> , 2011; Scuderi <i>et al.</i> , 2011, 2012; De Novellis <i>et al.</i> , 2012; Khasabova <i>et al.</i> , 2012; Kumar <i>et al.</i> , 2012; Romano and Lograno, 2012; Ambrosino <i>et al.</i> , 2013; Citraro <i>et al.</i> , 2013; Esposito <i>et al.</i> , 2014; Borrelli <i>et al.</i> , 2015; Hind <i>et al.</i> , 2015	LoVerme <i>et al.</i> , 2005, 2006; D'Agostino <i>et al.</i> , 2012; Di Paola <i>et al.</i> , 2012; Kumar <i>et al.</i> , 2012; Sasso <i>et al.</i> , 2012; Di Cesare Mannelli <i>et al.</i> , 2013; Paterniti <i>et al.</i> , 2013
Noladin ether	Sun <i>et al.</i> , 2007	Sun <i>et al.</i> , 2007	–	–
Virodhamine	Sun <i>et al.</i> , 2007	Sun <i>et al.</i> , 2007	–	–
Oleamide	Dionisi <i>et al.</i> , 2012	Dionisi <i>et al.</i> , 2012	–	–
Synthetic compounds				
WIN55,212-2	Sun <i>et al.</i> , 2007	Sun <i>et al.</i> , 2007	Downer <i>et al.</i> , 2012	–
ACEA	–	–	Palomba <i>et al.</i> , 2015	–

^aSun *et al.* (2007) found THC did not bind to PPAR α ; Liu *et al.* (2003) showed that AJA does not bind to or activate PPAR α .
–, no known data; ACEA, arachidonyl-2'-chloroethylamide; AEA, anandamide.

Table 2

 Current evidence for cannabinoid activation of PPAR γ

	Binding studies	Transcriptional activity	Blockade by selective antagonists	Use of siRNA
Phytocannabinoids and their derivatives				
THC	Granja <i>et al.</i> , 2012	O'Sullivan <i>et al.</i> , 2005	O'Sullivan <i>et al.</i> , 2005, 2006; Carroll <i>et al.</i> , 2012; Vara <i>et al.</i> , 2013	Vara <i>et al.</i> , 2013
THCV		^a		
CBD	O'Sullivan <i>et al.</i> , 2009a; Granja <i>et al.</i> , 2012	O'Sullivan <i>et al.</i> , 2009a; Hegde, 2015	O'Sullivan <i>et al.</i> , 2009a; Esposito <i>et al.</i> , 2011; De Filippis <i>et al.</i> , 2011; Ramer <i>et al.</i> , 2013; Scuderi <i>et al.</i> , 2014a; Hegde <i>et al.</i> , 2015; Hind <i>et al.</i> , 2016	Ramer <i>et al.</i> , 2013
AbnCBD			Bosier <i>et al.</i> , 2013	
AJA	Liu <i>et al.</i> , 2003; Ambrosio <i>et al.</i> , 2007	Liu <i>et al.</i> , 2003	Gonzalez <i>et al.</i> , 2012	–
CBG	Granja <i>et al.</i> , 2012	Granja <i>et al.</i> , 2012	–	–
CBC	Granja <i>et al.</i> , 2012	–	–	–
Cannabigerol quinone	Granja <i>et al.</i> , 2012	Granja <i>et al.</i> , 2012	–	–
Endocannabinoids				
AEA	Bouaboula <i>et al.</i> , 2005	Bouaboula <i>et al.</i> , 2005; Ahn <i>et al.</i> , 2015	Rockwell and Kaminski, 2004; Bouaboula <i>et al.</i> , 2005; O'Sullivan <i>et al.</i> , 2009b	–
2-AG	–	Rockwell <i>et al.</i> , 2006; Zhang <i>et al.</i> , 2014 ^a	Rockwell <i>et al.</i> , 2006; Du <i>et al.</i> , 2011; Zhang <i>et al.</i> , 2014	–
Endocannabinoid-like compounds				
NADA	–	O'Sullivan <i>et al.</i> , 2006 ^a	O'Sullivan <i>et al.</i> , 2009b	–
OEA	–	^a	–	–
PEA	–	O'Sullivan <i>et al.</i> , 2006 ^a	Costa <i>et al.</i> , 2008	–
Oleamide	Dionisi <i>et al.</i> , 2012	Dionisi <i>et al.</i> , 2012	–	–
Synthetic compounds				
Methanandamide	–	–	Eichele <i>et al.</i> , 2009	–
WIN55,212-2	–	O'Sullivan <i>et al.</i> , 2006; Fakhfouri <i>et al.</i> , 2012	Giuliano <i>et al.</i> , 2009; Mestre <i>et al.</i> , 2009; Fakhfouri <i>et al.</i> , 2012; Hong <i>et al.</i> , 2013; Payandemehr <i>et al.</i> , 2015	–
CP55,940	–	O'Sullivan <i>et al.</i> , 2006	–	–
HU331	Granja <i>et al.</i> , 2012	–	–	–
JWH015	^a	–	Vara <i>et al.</i> , 2013	Vara <i>et al.</i> , 2013

^aTHCV (O'Sullivan *et al.*, 2006); 2-AG (Kozak *et al.*, 2002; Ahn *et al.*, 2015), PEA (LoVerme *et al.*, 2005) or NADA (Ahn *et al.*, 2015) did not increase transcriptional activity of PPAR γ ; OEA did not bind to or activate PPAR γ (Fu *et al.*, 2003); JWH015 did not bind to PPAR γ (Vara *et al.*, 2013).

–, no known data; THCv, tetrahydrocannabivarin; AbnCBD, abnormal CBD; CBC, cannabigerol; CBG, cannabigerol; AEA, anandamide; NADA, N-arachidonoyl-dopamine.

to and activates the transcriptional activity of PPAR α and PPAR γ (Tables 1 and 2), and arachidonyl-2'-chloroethylamide, CP55940, HU331 and JWH015 activate PPAR γ (Table 2).

Cannabinoids, fatty acid binding proteins (FABPs) and PPARs

In the 2007 review, I speculated on the potential mechanisms of cannabinoid/PPAR interactions, suggesting that cannabinoids could bind directly to PPARs and be converted into PPAR-active metabolites or that activation of cell surface cannabinoid receptors initiates intracellular signalling cascades that lead to the activation of PPARs indirectly. Another possibility that has recently come to light is that cannabinoids may be actively transported to the nucleus and PPARs by FABPs. FABPs are intracellular lipid binding proteins, and binding to FABPs by ligands promotes nuclear localisation and interaction with PPAR α (Hughes *et al.*, 2015). Kaczocha *et al.* first showed in 2009 that anandamide was transported by FABP5 and 7 from the plasma membrane to FAAH for hydrolysis (Kaczocha *et al.*, 2009). They later showed that OEA is transported to the nucleus and to PPAR α by FABP5 and that FABP inhibition reduced the ability of OEA to activate PPAR α (Kaczocha *et al.*, 2012). THC and CBD were also recently shown to be transported intracellularly by FABPs (Elmes *et al.*, 2015), which may be the mechanism for their delivery to the nucleus for PPAR activation. Together, this suggests that FABPs can direct cannabinoids to enzymes for degradation or to the nucleus for PPAR activation. It is not yet clear what might be driving one pathway over another. FABP5 has also been shown to promote the cellular uptake and hydrolysis of anandamide, and that the metabolites derived from this are PPAR δ activators (Yu *et al.*, 2014), so activation of PPARs is still achieved despite anandamide degradation. On the other hand, inhibition of FABPs reduces inflammatory pain in mice, and this can be inhibited by CB $_1$ receptor or PPAR α antagonists (Kaczocha *et al.*, 2014), suggesting here that the FABP-direct degradation of endocannabinoids can also limit their ability to activate PPAR α .

Physiological responses to cannabinoids mediated by PPARs

From the first indication that cannabinoids activate PPARs, an important task has been to establish which of the physiological effects of cannabinoids might be mediated, at least in part, through activation of these receptors. This is particularly important to establish because the affinity of cannabinoids for PPARs tends to be in the micromolar range (although this is not dissimilar to the affinity of other endogenous ligands for PPARs, Kliewer *et al.*, 1997). Fortunately, many studies have now include tools to assess a role for PPAR activation (see Table 1 and 2 for references). Below is a summary of the evidence for PPAR activation as a mechanism of action (often in combination with some of the more traditional cannabinoid targets) for cannabinoids in some of the commonly recognized physiological effects of cannabinoids.

Neuroprotection

In terms of stroke models, a role for PPAR α and γ activation has been postulated in the actions of several cannabinoids. OEA reduces infarct volume after cerebral artery occlusion in mice, which is absent in PPAR α knockout mice (Sun *et al.*, 2007). Similarly, Zhou *et al.* (2012) showed that OEA improves neurological dysfunction and reduces infarct size and brain oedema after cerebral artery occlusion, which was inhibited by PPAR α antagonism. In an *in vitro* model of the blood-brain barrier (BBB), OEA increases monolayer resistance (i.e. reduces permeability) via PPAR α activation, and both OEA and PEA are able to reduce the hyperpermeability response to oxygen-glucose deprivation, sensitive to PPAR α antagonism (Hind *et al.*, 2015). In the same model, CBD is protective against increased permeability of the BBB associated with oxygen-glucose deprivation; however, in this case, the effects of CBD were sensitive to PPAR γ antagonism (Hind *et al.*, 2016).

In models of Alzheimer's disease, PEA blunts the expression of pro-inflammatory molecules in astrocytes in response to β -amyloid in a PPAR α -dependent, PPAR γ -independent manner (Scuderi *et al.*, 2011), and PEA decreases infiltrating astrocytes in hippocampal slices treated with β -amyloid, sensitive to PPAR α , but not PPAR γ , antagonism (Scuderi *et al.*, 2012). Chronic PEA administration also protects against the memory deficits induced by β -amyloid, which was absent in PPAR α -null mice (D'Agostino *et al.*, 2012). PEA protects against excitotoxicity in hippocampal cultures, which is blocked by a PPAR α but not PPAR γ antagonist (Koch *et al.*, 2011), and may be a mechanism by which PEA is protective in neurodegenerative disorders. This effect is not unique to PEA; 2-AG also inhibits β -amyloid formation by inhibiting the β -site amyloid precursor protein-cleaving enzyme, which was inhibited after PPAR γ knockdown (Zhang *et al.*, 2014). This study showed that inhibition of the degradation of 2-AG reduced inflammation and improved cognitive function in a mouse model of Alzheimer's disease, which was inhibited by a PPAR γ antagonist. CBD also protects against β -amyloid neurotoxicity and inflammation in rats, reduced by PPAR γ antagonism (Esposito *et al.*, 2011). In human neuronal cells, CBD reduces β -amyloid expression and increases amyloid precursor protein (APP) ubiquitination, which was inhibited by PPAR γ antagonism (Scuderi *et al.*, 2014a). *In vivo*, WIN55,212-2 reduces β -amyloid-induced neuroinflammation and improved memory function in rats, which was inhibited by antagonists of CB $_1$ and CB $_2$ receptors and PPAR γ (Fakhfoury *et al.*, 2012). Together, this suggests that activation of both PPAR α and PPAR γ by a range of cannabinoids is protective in models of Alzheimer's disease.

In a model of multiple sclerosis, increasing local levels of endocannabinoids by inhibiting their uptake (using UCM707) had neuroprotective effects against excitotoxicity, which could be inhibited by CB $_1$ and CB $_2$ receptor and PPAR γ antagonism (Loria *et al.*, 2010). In another animal model of inflammatory-demyelinating disease, the protective effects of WIN55,212-2 were inhibited by a PPAR α antagonist (Downer *et al.*, 2012). In this study, it was identified that WIN55,212-2, through PPAR α , activates the IFN- β promoter, which exerts a wide range of positive effects.

In models of epilepsy, anandamide and PEA decrease epileptic spike-wave discharge, which were inhibited by CB $_1$ receptor antagonism (both) and PPAR α antagonism

(PEA only) (Citraro *et al.*, 2013). WIN55,212-2 has anti-convulsant effects on GABA antagonist-induced seizures that are inhibited by CB₁ receptor, PPAR α and γ antagonists (Payandemehr *et al.*, 2015). THC has neuroprotective effects in a cell culture model of Parkinson's disease that was not inhibited by CB₁ receptor blockade, but was inhibited by a PPAR γ antagonist (Carroll *et al.*, 2012). PPAR γ activation after FAAH inhibition with URB597 also contributes to the anti-dyskinetic effects after chronic levodopa administration (Martinez *et al.*, 2015).

Reward

Up-regulation of local endocannabinoids by FAAH inhibition, or administration of OEA and PEA, inhibits neuronal responses in the reward area of the brain to nicotine but not cocaine or morphine (Luchicchi *et al.*, 2010), which was sensitive to both CB₁ receptor and PPAR α antagonism (Melis *et al.*, 2008; Luchicchi *et al.*, 2010). Nicotine reward was also reduced by FAAH inhibition in primates and the effect of FAAH inhibition was reversed by PPAR α antagonism (Justinova *et al.*, 2015), suggesting that FAAH inhibitors might be useful smoking cessation tools. A similar effect on nicotine reward mediated by PPAR α was seen in response to methyl OEA, a long-lasting form of OEA, or to PPAR α agonists (Mascia *et al.*, 2011).

Memory and cognition

Mazzola *et al.* (2009) showed that memory acquisition in rats is enhanced by the FAAH inhibitor URB597, which was sensitive to PPAR α antagonism. Campolongo *et al.* (2009) showed that OEA administration also has a memory-enhancing effect that was absent in PPAR α -null mice. In Alzheimer's disease models, PEA protects against memory deficits, which was absent in PPAR α -null mice (D'Agostino *et al.*, 2012), and WIN55,212-2 improves memory function, which was inhibited by a PPAR γ antagonist (Fakhfour *et al.*, 2012). Low doses of THC (administered either before or after the insult) also protect against the cognitive damage (object recognition) induced by inflammation, and this effect was inhibited by a CB₁ receptor or PPAR γ antagonist (but not by CB₂ receptor antagonism) (Fishbein-Kaminietsky *et al.*, 2014).

Analgesia

Several studies have shown that PEA has analgesic effects *in vivo* in several models of pain behaviour that are inhibited by PPAR α antagonists or are absent in PPAR α knockout mice (LoVerme *et al.*, 2005; de Novellis *et al.*, 2012; Sasso *et al.*, 2012; Di Cesare Mannelli *et al.*, 2013). The PPAR α -mediated analgesic effects of PEA have also been demonstrated in peripheral sensory nerve cells, which additionally involved the activation of TRPV1 channels, but not CB₁ or CB₂ receptors (Ambrosino *et al.*, 2013). A PEA analogue, palmitoylallylamide, also reduces hypersensitivity in neuropathic pain that was inhibited by antagonists of CB₁ and CB₂ receptors and of PPAR α (Wallace *et al.*, 2007). By contrast, Costa *et al.* (2008) found that the analgesic effects of PEA in neuropathic pain involved CB₁ receptors, TRPV1 channels and PPAR γ , but not PPAR α or CB₂ receptors.

Up-regulation of local endocannabinoid levels by inhibition of FAAH with URB597 induces analgesia in an inflammatory pain model, and this was inhibited by a PPAR α antagonist but

not a CB₁ receptor antagonist (Sagar *et al.*, 2008) or a PPAR γ antagonist (Jhaveri *et al.*, 2008). In the Jhaveri study, URB597 increased local levels of anandamide and 2-AG, so either ligand could be activating PPAR α . Interestingly, Jhaveri *et al.* (2008) also showed that COX2 inhibition increased local PEA levels and caused analgesia that was inhibited by a PPAR α antagonist. Another FAAH inhibitor, ST4070, also reduces neuropathy, increases anandamide and 2-AG levels and is sensitive to antagonists of CB₁, receptors, TRPV1 channels and PPAR α antagonism (Caprioli *et al.*, 2012). A similar effect was seen with an inhibitor of *N*-acyl ethanolamine acid amidase (ARN077), which was found to have anti-nociceptive effects in rodent models that were inhibited by a PPAR α antagonist (but not CB₁ or CB₂ receptor antagonists) and absent in PPAR α knockout mice, associated with an increase in OEA and PEA levels (Khasabova *et al.*, 2012; Sasso *et al.*, 2013). It has also been shown that inhibition of FABPs reduces inflammatory pain in mice, and this effect was inhibited by antagonists of CB₁ receptors or PPAR α , which was associated with an up-regulation of anandamide (but not 2-AG, OEA or PEA), and anandamide was suggested as the activating ligand (Kaczocha *et al.*, 2014).

Anti-tumour effects of cannabinoids

In many cancer cell lines, there is much evidence now to show that cannabinoids induce apoptosis via PPAR γ . This has been shown for WIN55,212-2 in liver cancer cells (Giuliano *et al.*, 2009; Hong *et al.*, 2013), for methanandamide in cervical carcinoma cells and lung carcinoma cells (Eichele *et al.*, 2009), for CBD in human lung cancer cells (Ramer *et al.*, 2013) and for THC and JWH015 (a CB₂ receptor agonist) in liver cancer cells (Vara *et al.*, 2013). The anti-tumour effect of THC in human breast cancer cells involved the activation of both PPAR α and γ (Takeda *et al.*, 2013, 2014). Collectively, this suggests that PPAR activation is involved in the anti-tumour effects of cannabinoids. In support of this, there is increasing evidence that the thiazolidinedione class of PPAR γ ligands, normally used in the treatment of diabetes, may have a potential new role in the treatment of cancer (Joshi *et al.*, 2014).

Cardiovascular system

THC causes time-dependent, PPAR γ -dependent vasorelaxation in rat isolated arteries (the aorta and superior mesenteric artery) that is dependent on production of NO and hydrogen peroxide and on superoxide dismutase activity (O'Sullivan *et al.*, 2005). THC also enhances vasodilator responses in isolated arteries, which could be inhibited by a PPAR γ antagonist (O'Sullivan *et al.*, 2006). A similar time-dependent and PPAR γ -sensitive vasorelaxant response in the rat aorta was also observed in response to CBD (O'Sullivan *et al.*, 2009a) and the endocannabinoids anandamide and *N*-arachidonoyl dopamine, but not PEA (O'Sullivan *et al.*, 2009b). Romano & Lograno (2012) also showed a time-dependent vasorelaxant response to anandamide and PEA in the bovine ophthalmic artery, but this effect was inhibited by a PPAR α , but not a PPAR γ , antagonist. Kumar *et al.* (2012) showed that PEA increases aqueous humour outflow in porcine eyes, which is inhibited by PPAR α antagonism or knockdown.

In a model of multiple sclerosis, WIN55,212-2 suppresses the increased intercellular adhesion molecule and vascular cell adhesion molecule (VCAM) in brain endothelium,

sensitive to PPAR γ , but not CB $_1$ or CB $_2$ receptor antagonists (Mestre *et al.*, 2009). CBD also reduces VCAM in human brain microvascular endothelial cells via PPAR γ (Hind *et al.*, 2016). An analogue of OEA, (Z)-(S)-9-octadecenamide, N-(2-hydroxyethyl, 1-methyl), decreases the expression of VCAM and ICAM and monocyte adhesion in response to inflammation in HUVECs, which was antagonized by PPAR α (Chen *et al.*, 2011). A reduction in these markers of endothelial activation may be a result of the anti-inflammatory effects of PPAR activation.

Suppression of PPAR α is postulated to mediate the cardioprotective effects of WIN55,212-2 in doxorubicin-induced cardiotoxicity (Rahmatollahi *et al.*, 2015).

Regulation of satiety, feeding and metabolism

Fu *et al.* (2003, 2005) first showed that the anorectic and weight-reducing effects of OEA were absent in PPAR α knockout mice, and OEA administered daily reduced serum cholesterol levels in rat and mouse models of obesity. Guzman *et al.* (2004) also showed that the lipolytic effect of OEA *in vivo* was absent in PPAR α knockout mice. Analogues of OEA with a high affinity for PPAR α cause similar reductions in food intake (Astarita *et al.*, 2006). The anorexic effects of OEA are mediated centrally by oxytocin signalling, which was absent in PPAR α knockout mice (Gaetani *et al.*, 2010; Romano *et al.*, 2013). A peripherally restricted anandamide uptake inhibitor, AM404, also reduced feeding through a PPAR α -dependent mechanism (Reyes-Cabello *et al.*, 2012). More recently, a potential role for PPAR γ has been identified in the regulation of leptin activity by CB $_1$ receptors in hypothalamic neurons (Palomba *et al.*, 2015).

The anti-nausea effects of FAAH inhibition are mediated by PPAR α (Rock *et al.*, 2015). Interesting, while the effects of PF3845 were inhibited by a PPAR α antagonist but not a CB $_1$ antagonist, the effects of URB597 were inhibited by a CB $_1$ receptor but not a PPAR α antagonist, suggesting that these FAAH inhibitors are potentially causing a differential effects on endocannabinoid tone (albeit with the same end point of reduced nausea). No studies have yet examined whether PPAR α plays a role in the anti-nausea effects of other cannabinoids.

Anti-inflammatory effects

The PPAR-mediated anti-inflammatory effects of some cannabinoids in the brain have already been outlined above, and there are many further studies showing PPAR-mediated anti-inflammatory effects of cannabinoids. This was probably first demonstrated by Liu *et al.* (2003) who showed that AJA inhibits the promoter activity of IL-8, a pro-inflammatory cytokine, in a PPAR γ -dependent manner. AJA also inhibits skin fibrosis in mice overexpressing transforming growth factor β , sensitive to PPAR γ antagonism (Gonzalez *et al.*, 2012). Rockwell and Kaminski (2004) found that anandamide inhibits the secretion of the pro-inflammatory cytokine, IL-2, in a CB $_1$ /CB $_2$ receptor-independent manner that could be prevented by a PPAR γ antagonist. 2-AG also inhibited IL-2 secretion through the suppression of pro-inflammatory transcription factors, sensitive to PPAR γ antagonism (Rockwell *et al.*, 2006). 2-AG also decreases the expression of COX2 in response to IL-1 β or LPS, sensitive to PPAR γ antagonism (Du *et al.*, 2011). Furthermore, the 2-AG metabolite 15d-PGJ $_2$ -glycerol ester has anti-inflammatory

actions mediated by PPAR γ (Raman *et al.*, 2011). Up-regulation of local endocannabinoid levels by inhibition of FAAH or inhibition of the putative anandamide transporter significantly potentiated the circulating cytokine response to LPS in rats, and this effect was reduced by antagonism of CB $_1$ and CB $_2$ receptors, TRPV1 channels and PPAR γ (Roche *et al.*, 2008).

Other studies have also demonstrated a role for PPAR α in mediating the anti-inflammatory effects of some cannabinoids. Both OEA and PEA are anti-inflammatory in chemically induced oedema, which were absent in PPAR α knockout mice (LoVerme *et al.*, 2005). PEA also reduces inflammation, neutrophil infiltration, pro-inflammatory cytokines and NO synthase activity after spinal cord trauma, and this effect was absent in PPAR α knockout mice and reduced by antagonism of PPAR α and δ (Paterniti *et al.*, 2013). PEA also decreases intestinal inflammation induced by ischaemia/reperfusion injury, which was reduced in PPAR α knockout mice (Di Paola *et al.*, 2012), and decreases the pathology of colitis in two different mouse models, which could be inhibited by CB $_2$ receptors, GPR55 and PPAR α antagonists (Borrelli *et al.*, 2015; Esposito *et al.*, 2014). In an *in vitro* model of intestinal permeability induced by inflammation, we found that OEA and PEA were able to positively affect the hyperpermeability, which could be inhibited by PPAR α antagonism (Karwad *et al.*, 2014). In addition to the anti-inflammatory role of PPAR α activation in the gut, another study has shown that the anti-inflammatory effects of CBD in the gastrointestinal system in LPS-treated mice are PPAR γ mediated (De Filippis *et al.*, 2011). Similarly, Hegde *et al.* (2015) showed that the anti-inflammatory effects of CBD via the induction of myeloid-derived suppressor cells were inhibited by PPAR γ antagonism.

Physiological responses to cannabinoids that are PPAR independent

While there is evidence for PPAR activation by cannabinoids to be involved in many aspects of cannabinoid responses, there are studies equally demonstrating that PPAR activation does not underpin the effects of cannabinoids in their particular experimental model, as summarized in Table 3. At this stage, it is unclear as to why some physiological responses are mediated by PPARs for some cannabinoids and not others, despite an apparent similar ability to activate PPARs (Tables 1 and 2). For example, the effects of CBD at the BBB are inhibited by PPAR γ antagonism (Hind *et al.*, 2016), but the effects of anandamide are not (Hind *et al.*, 2016), despite the fact that anandamide is known to activate PPAR γ . Similarly, the effects of OEA and PEA on intestinal permeability are mediated by PPAR α (Karwad *et al.*, 2014), although the effects of anandamide and 2-AG in the same cells are not, instead acting via CB $_1$ (Alhamboruni *et al.*, 2010, 2012). There are many factors that could be influencing the interactions between cannabinoids and PPARs. These include whether they also activate cell surface or other receptors, their metabolism, binding to FABPs and their intracellular fate, which FABP they preferentially bind and the recruitment of PPAR co-activators or repressors. All these many confounding factors require further investigation.

Table 3

Physiological responses to cannabinoids that known to be PPAR-independent

	Physiological response	Isoform not involved	Reference
Endocannabinoids			
AEA	Modulation of intestinal permeability	PPAR α or γ	Alhamoruni <i>et al.</i> , 2010, 2012
	Reaction time tasks	PPAR α	Panlilio <i>et al.</i> , 2009
	Antiepileptic effect	PPAR α	Citraro <i>et al.</i> , 2013
	Modulation of BBB permeability	PPAR α or γ	Hind <i>et al.</i> , 2015
	Time-dependent vasorelaxant	PPAR γ	Romano and Lograno, 2012
Endocannabinoid-like compounds			
2-AG	Modulation of intestinal permeability	PPAR α or γ	Alhamoruni <i>et al.</i> , 2010, 2012
OEA	Upper GI transit	PPAR α	Cluny <i>et al.</i> , 2009
	Gastric emptying	PPAR α	Aviello <i>et al.</i> , 2008
	Modulation of cocaine-induced behaviour	PPAR α	Bilbao <i>et al.</i> , 2013
PEA	Neuroprotection	PPAR γ	Koch <i>et al.</i> , 2011; Scuderi <i>et al.</i> , 2011; Scuderi <i>et al.</i> , 2012
	Analgesia in neuropathic pain	PPAR α	Costa <i>et al.</i> , 2008
	Time-dependent vasorelaxant in the bovine ophthalmic artery	PPAR γ	Romano and Lograno, 2012
	Intestinal motility	PPAR α	Capasso <i>et al.</i> , 2014
	Decreased contact dermatitis	PPAR α	Petrosino <i>et al.</i> , 2010
Noladin ether	Anti-proliferative effect	PPAR γ	Nithipatikom <i>et al.</i> , 2011
Increasing local activity of the endocannabinoid system			
AM404	Decreased food intake	PPAR α	Reyes-Cabello <i>et al.</i> , 2012
URB597	Analgesia in an inflammatory pain model	PPAR γ	Jhaveri <i>et al.</i> , 2008
URB597	Anti-nausea effects	PPAR α	Rock <i>et al.</i> , 2015
Phytocannabinoids			
THC	Modulation of intestinal permeability	PPAR α or γ	Alhamoruni <i>et al.</i> , 2010, 2012
CBD	Modulation of intestinal permeability	PPAR α or γ	Alhamoruni <i>et al.</i> , 2010, 2012
	Enhancement of vasorelaxation in diabetic arteries	PPAR γ	Wheal <i>et al.</i> , 2014
	Vasorelaxation of human small mesenteric arteries	PPAR γ	Stanley <i>et al.</i> , 2015
Synthetic cannabinoids			
Methanandamide	Suppressed nicotine-induced excitation	PPAR α	Melis <i>et al.</i> , 2008
AJA	Anti-inflammatory effects	PPAR γ	Johnson <i>et al.</i> , 2007; Parker <i>et al.</i> , 2008

AEA, anandamide; GI, Gastrointestinal; ECS, endocannabinoid system.

Conclusion

The aims of this review were to update the evidence that cannabinoids have “gone nuclear” and to establish whether activation by cannabinoids of the PPARs, a major class of nuclear hormone receptors, plays a role in their physiological effects (O'Sullivan, 2007; O'Sullivan, 2013). Although our knowledge in this area has significantly increased, there are still many cannabinoids whose activity at PPARs remains unknown. For example, there is little known about the effects of phytocannabinoids on PPAR α and the potential role for PPAR δ activation by cannabinoids. We do now know that many of the well-recognized

responses to cannabinoids such as neuroprotection and analgesia are at least partly mediated by the activation of PPARs, although this is better investigated for some cannabinoids, such as OEA and PEA, than others. Despite the fact that anandamide and 2-AG bind to both PPAR α and PPAR γ , few studies have probed this as a mechanism of action for these endocannabinoids, possibly because much of the characterisation of these compounds was carried out before PPARs were proposed as additional targets of cannabinoids. Finally, there are also many PPAR-independent effects of cannabinoids, and the many factors that could be influencing the interactions between cannabinoids and PPARs remain to be established.

Conflict of interest

The author declares no conflicts of interest.

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