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REVIEW ARTICLE

PPARs and pain

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Chronic pain is a common cause of disability worldwide and remains a global health and socio-economic challenge. Current analgesics are either ineffective in a significant proportion of patients with chronic pain or associated with significant adverse side effects. The PPARs, a family of nuclear hormone transcription factors, have emerged as important modulators of pain in preclinical studies and therefore a potential therapeutic target for the treatment of pain. Modulation of nociceptive processing by PPARs is likely to involve both transcription-dependent and transcription-independent mechanisms. This review presents a comprehensive overview of preclinical studies investigating the contribution of PPAR signalling to nociceptive processing in animal models of inflammatory and neuropathic pain. We examine current evidence from anatomical, molecular and pharmacological studies demonstrating a role for PPARs in pain control. We also discuss the limited evidence available from relevant clinical studies and identify areas that warrant further research.

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Abbreviations

ACC, anterior cingulate cortex; AEA, anandamide; CCI, chronic constriction injury; CFA, complete Freund's adjuvant; DRG, dorsal root ganglion; EMSA, electrophoretic mobility shift assay; FAAH, fatty acid amide hydrolase; iNOS, inducible NOS; OEA, *N*-oleoylethanolamide; PAG, periaqueductal grey; lPAG, lateral PAG; VlPAG, ventrolateral PAG; PEA, *N*-palmitoylethanolamide; PPRE, peroxisome proliferator response element; RXR, retinoid X receptor; RVM, rostroventromedial medulla; SD, Sprague–Dawley; VTA, ventral tegmental area; WKY, Wistar-Kyoto

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Peroxisome proliferator-activated receptors

The **PPARs** are ligand-dependent transcription factors that belong to the nuclear hormone superfamily of receptors. Three major isoforms have been identified: **PPARα**, cloned from mouse liver (Issemann and Green, 1990), **PPARβ**/δ and **PPARγ**, both cloned from *Xenopus* (Dreyer *et al*., 1992). These three isoforms share a common structure, typified by the presence of a highly conserved DNA binding domain, with two zinc finger motifs, that recognize the peroxisome proliferator response element (PPRE) in the promoter regions of target genes (Desvergne and Wahli, 1999). They also contain two transcription activation domains; ligand independent AF-1 in the N-terminal domain (Delerive *et al*., 2002) and the AF-2 in the C-terminal domain, which is ligand-dependent and has a large ligand binding domain. This large ligand binding domain makes it possible for PPARs to interact with a wide array of synthetic and natural lipid ligands.

PPARs exist as heterodimers with the retinoid X receptor (**RXR**), bound to co-repressor proteins in the inactive state. Upon ligand activation, the co-repressors dissociate from the PPAR/RXR complex, allowing for the recruitment of co-activators. The activated PPAR/RXR-co-activator complex subsequently binds to specific DNA sequences or PPRE, resulting in the transcriptional activation of target genes (Green *et al*., 1992, Tugwood *et al*., 1992). Genes regulated by PPARs *via* this PPRE-dependent mechanism are mainly involved in lipid and lipoprotein metabolism (Tugwood *et al*., 1992). Alternate mechanisms of action that do not involve PPRE binding have been reported, especially for PPARα, which has known anti-inflammatory effects (Delerive *et al*., 2001). These latter mechanisms involve inhibition of **NF-κB** and AP-1 inflammatory signalling and the consequent trans-repression of pro-inflammatory genes such as inducible NOS (**iNOS**), **COX-2** and **TNF-α** (Crisafulli and Cuzzocrea, 2009, Cuzzocrea *et al*., 2008, Delerive *et al*., 2000). These anti-inflammatory consequences of PPARα activation are fundamental to the role of this receptor in modulating both inflammatory and neuropathic pain as discussed later.

PPARs are widely distributed in mammalian tissues, including the peripheral and CNSs (Braissant *et al*., 1996, Moreno *et al*., 2004) (Table 1), and are activated by a variety of endogenous compounds derived from saturated and unsaturated fatty acid, of which **N-palmitoylethanolamide** (PEA) (LoVerme *et al*., 2005) and **N-oleoylethanolamide** (OEA) (Fu *et al*., 2003) remain the best characterized to date. The ubiquitous distribution of PPARs also reflects their roles in many physiological processes, including an emerging role as key modulators in nociceptive processing. In particular, and as reviewed below, anatomical, molecular and pharmacological studies suggest that the PPAR signalling system may be a viable therapeutic target for the treatment of chronic pain and its comorbidity with stress-related psychiatric disorders.

Table 1

Expression of mRNA or protein for PPAR isoforms within neuroanatomical loci involved in pain

	Neuroanatomical locus	PPARα	PPARβ/δ	PPARγ
Peripheral	Dorsal root ganglion	✓[b,c]	?	?
	C fibres	?	?	?
	Aδ fibres	?	?	?
	Aβ fibres	?	?	?
Spinal	Spinal cord	✓[*d]	✓[d]	✓[a,d,g]
Supraspinal	Frontal cortex	✓[d]	✓[d]	✓[d]
	Pre-frontal cortex (PFC)	✓[e]	✓[e]	✓[e]
	Hippocampus	✓[d]	✓[d]	✓[d]
	Thalamus	✓[d]	✓[d]	✓[d]
	Hypothalamus	✗[d]	✓[d]	✓[d]
	Basal ganglia	✓[d,e]	✓[d,e]	✓[d,e]
	Amygdala	✓[e]	✓[e]	✓[e]
	PAG	✓[f]	?	✓[f]
	Rostroventral medulla (RVM)	?	?	?
	Ventral tegmental area (VTA)	✓[e]	✓[e]	✓[e]

✓, present; ✗, absent; ?, expression not known.
[a]Not expressed in all laminae.
[b]D'Agostino *et al*., 2009.
[c]LoVerme *et al*., 2006.
[d]Moreno *et al*., 2004.
[e]Warden *et al*., 2016.
[f]Okine *et al*., 2017.
[g]Churi *et al*., 2008.

Expression of PPARs in key components of the pain pathway

A role for PPAR signalling in pain processing is suggested by studies demonstrating the presence of the different PPAR isoforms at key peripheral, spinal and supraspinal sites involved in pain processing (Table 1; Figure 1). Within the periphery, PPARα protein is expressed in the dorsal root ganglion (DRG) (LoVerme *et al.*, 2006), although the relative distribution within DRG sub-nuclei remains unreported. Unlike PPARα, to our knowledge, the expression of PPARβ or PPARγ in the DRG remains unexplored. Despite the paucity of data on the distribution pattern of PPARα on nociceptive primary afferents (Aδ-fibres and C-fibres), the reported analgesic effects of PPARα agonists, administered locally or peripherally, in animal models of inflammatory and neuropathic pain (see Table 2 for comprehensive list) suggest a modulatory influence on peripheral nociceptive afferents such that PPARα activation in the DRG results in the suppression or silencing of nociceptive afferent fibre firing. However, the validation of this hypothesis requires further characterization of PPARα in DRG nuclei using double-labelling immunohistochemistry or *in situ* hybridization techniques.

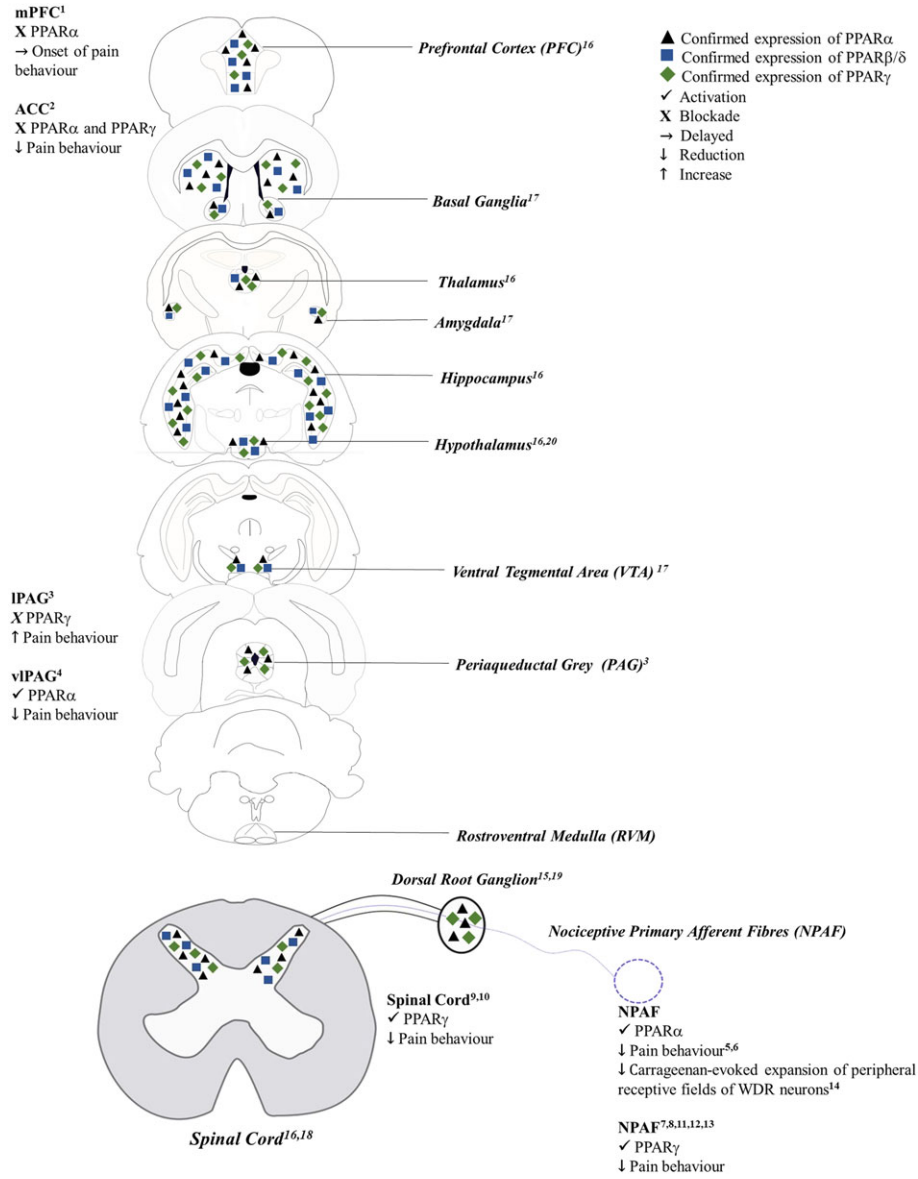

Figure 1

Anatomical localization of PPAR isoforms in key components of the pain pathway and their role in pain modulation. (1) Okine *et al.* (2014); (2) Okine *et al.* (2017); (3) Okine *et al.* (2016); (4) De Novellis *et al.* (2012); (5) LoVerme *et al.* (2006); (6) Russo *et al.* (2007); (7) Hasegawa-Moriyama *et al.* (2013); (8) Mansouri *et al.* (2017a, b); (9) Churi *et al.* (2008); (10) Griggs *et al.* (2015); (11) Saito *et al.* (2016); (12) Hasegawa-Moriyama *et al.* (2012); (13) Takahashi *et al.* (2011); (14) Sagar *et al.* (2008); (15) D'Agostino *et al.* (2009); (16) Moreno *et al.* (2004); (17) Warden *et al.* (2016); (18) Churi *et al.* (2008); (19) Maeda *et al.* (2008); (20) Chakravarthy *et al.* (2007).

Table 2

Summary of pharmacological studies investigating the role of PPARs in animal models of pain

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Inflammatory	Carrageenan	PEA and GW7647 (PPARα agonist)	2 μL per mouse (i.c.v) 0.3 μL (spinal)	i.c.v and spinal	Swiss mice	Reduced hyperalgesia in mice *via* inhibition of pro-inflammatory signalling in the carrageenan model of inflammatory pain. The results were mimicked by the PPARα agonist (GW7647).	D'Agostino *et al.* (2009)
Inflammatory	Subcutaneous carrageenan	PEA	200, 400 and 800 $\mu g \cdot mL^{-1}$	Subcutaneous	Wistar rats	Treatment with PEA reduced allodynia evaluated by Von Frey.	De Filippis *et al.* (2011)
Inflammatory	Carrageenan	PFOA (PPARα agonist) and rosiglitazone (PPARγ agonist)	100 $mg \cdot kg^{-1}$	Systemic	Sprague–Dawley rats	Pretreatment with either drug inhibited carrageenan-induced oedema in a dose-dependent manner and also reduced carrageenan-induced hyperalgesia.	Taylor *et al.* (2002)
Inflammatory	Carrageenan	Rosiglitazone and **15d-PGJ$_2$** (PPARγ agonist)	0–5 to 50 mg (rosiglitazone) and 50–200 mg (15d-PGJ2)	i.c.v	Sprague–Dawley rats	i.c.v. administration of the drugs dose-dependently reduced behavioural withdrawal responses to noxious heat. The administration of antagonists (**BADGE** and GW9662) reversed the anti-hyperalgesic effects.	Morgenweck *et al.* (2009)
Inflammatory	Carrageenan and collagen-induced arthritis	Adelmidrol (PEA analogue)	10 $mg \cdot kg^{-1}$	Intraperitoneal	Sprague–Dawley rats	The administration of adelmidrol produced a significant inhibition in the development of carrageenan-induced and collagen-induced thermal and mechanical allodynia. This anti-allodynic effect was reversed by GW9662 (PPARγ antagonist).	Impellizzeri *et al.* (2016)
Inflammatory	Carrageenan	**URB597** (FAAH inhibitor)	25 and 100 μg	Intraplantar	Sprague–Dawley rats	The administration of URB597 attenuated the hyperalgesia induced by carrageenan. GW6471 (PPARα antagonist) reversed this effect.	Jhaveri *et al.* (2008)
Inflammatory	Carrageenan	GW0742 and **ATRA**(PPARβ/δ agonist)	0.1 $mg \cdot kg^{-1}$ (GW0742) and 5 $mg \cdot kg^{-1}$ (ATRA)	Intraperitoneal	Wistar rats	The administration of both drugs has reduced mechanical and thermal hyperalgesia induced by carrageenan. The co-treatment with a PPARβ/δ antagonist (GSK0660) has blocked the effects of the drugs.	Gill *et al.* (2013)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Inflammatory	Formalin	GW7647 (PPARα agonist)	0.1–10 μg/10 μL	Intraplantar	Swiss mice	GW7647 inhibited phase I and phase II pain behaviour in the formalin-induced inflammatory pain model at the highest dose.	Russo *et al*. (2007)
Inflammatory	Formalin and carrageenan	PEA	0.01–50 μg/200 μL	Intraperitoneal	Swiss mice	Reduction in both early and late phases of formalin-induced nociception by PEA at 5 and 50 mg per paw. PPARα knockout animals failed to respond to PEA compared to wild-type animals. The injection of carrageenan resulted in a significant reduction of mechanical and thermal threshold values. Both hyperalgesic parameters were strongly reduced by PEA (50 mg).	Sasso *et al*. (2012)
Inflammatory	Formalin	GW7647 (PPARα agonist) and GW6471 (PPARα antagonist)	10 μg (GW7647); 10 μg (GW6471)	Intra-mPFC	Sprague–Dawley rats	Intra-mPFC administration of GW6471, but not GW7647, resulted in delayed onset of the early second phase of formalin-evoked nociceptive behaviour. Formalin-evoked nociceptive behaviour was associated with significant reductions in mPFC levels of endogenous PPARα ligands (PEA and OEA).	Okine *et al*. (2014)
Inflammatory	Formalin	GW6471 (PPARα antagonist) and GW9662 (PPARγ antagonist)	3 nmol–5 μL (GW6471); 36 nmol–5 μL (GW9662)	Intra-ACC	Sprague–Dawley rats	Both antagonists significantly reduced formalin-evoked nociceptive behaviour, suggesting facilitatory/ permissive roles for these receptors in the ACC in inflammatory pain.	Okine *et al*. (2017)
Inflammatory	Formalin	GW9662 (PPARγ antagonist)	14.4 nmol/0.2 μL	Intra-lPAG	Sprague–Dawley rats and Wistar-Kyoto rats	Pharmacological blockade of PPARγ in the lPAG enhanced formalin-evoked nociceptive behaviour in WKY, but not SD, rats.	Okine *et al*. (2016)

continues

Table 2

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Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Inflammatory	Formalin and carrageenan	Fenofibrate and pioglitazone	100 or 300 mg·kg^{-1} (fenofibrate; acute and chronic – 7 days); 25, 50 or 100 mg·kg^{-1} (acute pioglitazone)	*Per os* (p.o.) – fenofibrate Intraperitoneal – pioglitazone	Swiss mice and Wistar rats	Chronic and acute administration of fenofibrate and acute administration of pioglitazone did not inhibit nociceptive responses of mice in the hot plate or in the first phase of the formalin test. The chronic treatment with fenofibrate and acute administration of pioglitazone (same doses) attenuated the second phase of the formalin-induced nociceptive response. The prolonged treatment with fenofibrate also attenuated the initial phase of the carrageenan-induced nociceptive behaviour in rats.	Oliveira *et al.* (2007)
Inflammatory	Complete Freund's adjuvant (CFA)-induced inflammation	Rosiglitazone	0.3, 3 or 30 μg	Intraplantar	C57BL6 mice	Hyperalgesia to mechanical stimuli was dose-dependently attenuated on days 5 and 7 after the procedure in mice that received rosiglitazone, which was reversed to the level of vehicle-injected mice by coadministration of GW9662. In contrast to the effects of rosiglitazone on mechanical stimuli, rosiglitazone had little effect on withdrawal latency to heat stimuli.	Hasegawa-Moriyama *et al.* (2013)
Inflammatory	Formalin	GW9662 and pioglitazone	2 mg·kg^{-1} (GW9662) and 10, 20, 30 or 50 mg·kg^{-1} (pioglitazone)	Intraperitoneal	Wistar rats	Pioglitazone at doses 30 and 50 mg·kg^{-1} significantly inhibited the flinching behaviour in phase 1 and, at dose 30 mg·kg^{-1}, in phase 2. GW9662 had no effect in nociceptive behaviour *per se*, but it attenuated antinociceptive effects of the combined treatment of simvastatin and pioglitazone.	Mansouri *et al.* (2017a, b)
Inflammatory	Formalin	GW9662 and pioglitazone	2 mg·kg^{-1} (GW9662) and 10, 20, 30 or	Intraperitoneal and intraplantar	Wistar rats	Both routes of pioglitazone administration produced antinociception in both phases	Mansouri *et al.* (2017a, b)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
			50 mg·kg^{-1} (pioglitazone)			of formalin-induced pain. Antinociception caused by i.p. and i.pl. pioglitazone was blocked by GW-9662 at doses 2 mg·kg^{-1} (i.p.) and 3 μg per paw (i.pl.).	
Inflammatory	Complete Freund's adjuvant (CFA)-induced	–	–	–	Wistar rats	PPARα was rapidly activated in lumbar spinal cord after CFA intraplantar injection.	Benani *et al.* (2004)
Inflammatory	Formalin, carrageenan and writhing test	Oleanoic acid (OA)	10, 20 and 40 mg·kg^{-1}	Oral	Swiss mice	OA treatment inhibits acetic acid-induced abdominal writhing in mice. OA alone did not produce a significant effect on the first phase of the formalin test but reduced the number of paw licks in the second phase of the formalin test.	Vasconcelos *et al.* (2006)
Inflammatory	Formalin	PEA and GW6471	0.2 and 2 mg·kg^{-1} (GW6471 i.p.), 0.2 or 1 g/5 μL per mouse (GW6471 i.t.), 1 μg/20 μL per mouse (GW6471 i.pl.) 1 or 3 mg·kg^{-1} (PEA i.p.)	Intraperitoneal (GW6471 was also administered intraplantar and intrathecal)	ICR mice and −/−α7 mice (C57BL/6 background)	GW6471 blocks and PEA potentiates the antinociceptive effects of α7 nAChR full agonist. PEA and GW6471 alone do not affect formalin-evoked nociceptive responses.	Donvito *et al.* (2017)
Inflammatory	Formalin – Tempomandibular joint (TMJ)	15d-PGJ$_2$ and GW9662	0.3, 1 or 3 ng/15 μL per TMJ (GW9662) 100 ng/15 μL per TMJ (15d-PGJ2)	Intra-TMJ	Wistar rats	Treatment with 15d-PGJ$_2$ attenuated formalin-evoked nociceptive behaviour in the TMJ. This effect was blocked by GW9662 (PPARγ antagonist).	Pena-dos-Santos *et al.* (2009)
Inflammatory	Carrageenan	URB597, GW6471 and WY14643 (PPARα agonist)	25 μg in 50 μL (URB597) 30 μg in 50 μL (GW6471) 100 μg in 50 μL (WY14643)	Intraplantar	Sprague–Dawley rats	GW6471 completely abolished the inhibitory effects of URB597 on the carrageenan-evoked expansion of receptive fields (8 g) and WY14643 significantly attenuated carrageenan-evoked expansion of peripheral receptive fields of WDR neurons.	Sagar *et al.* (2008)
Inflammatory	Carrageenan and formalin –	15d-PGJ$_2$ and GW9662	30–300 ng per paw (15d-PGJ$_2$)	Intraplantar or intra-TMJ	Wistar rats	15d-PGJ$_2$ inhibits the mechanical hypernociception induced carrageenan in the	Napimoga *et al.* (2007)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
	Tempomandibular joint (TMJ)					hind paw and formalin in the TMJ. These effects were blocked by GW9662.	
Inflammatory	Carrageenan	PEA and siRNA for PPARα	1.0 $\mu g \cdot h^{-1}$	i.c.v.	Sprague–Dawley rats	Lower PPARα expression was observed in the spinal cord of high fat-fed rats. PEA significantly attenuated thermal and mechanical hyperalgesia in HF-fed rats. Intrathecal administration of PPARα siRNA completely abolished the effects of i.c.v. PEA on pain sensitivity.	Wang *et al.* (2014)
Inflammatory	Carrageenean (diet-induced obesity)	siRNA for PPARα	10 μL	Intrathecal	Sprague–Dawley rats	Knockdown of spinal PPARα eradicated the beneficial effects of ursolic acid on thermal hyperalgesia and paw oedema, and reversed the spinal cord inflammatory response.	Zhang *et al.* (2016)
Neuropathic and inflammatory	Chronic constriction injury of sciatic nerve (CCI), Freund's adjuvant and carrageenan	PEA and GW7647 (PPARα agonist)	PEA (50 mg) and GW7647 (50 mg); PEA (20 $mg \cdot kg^{-1}$) s.c.	Intraplantar and subcutaneous	Swiss mice	PEA reduced formalin-induced pain at i.pl. doses; GW7647 and PEA reduced hyperalgesic responses in the CCI model of neuropathic pain; acute administration of GW7647 and PEA reduced hyperalgesic responses in the complete Freund's adjuvant and carrageenan models of inflammatory pain.	LoVerme *et al.* (2006)
Inflammatory and neuropathic	Chronic constriction injury (CCI) and acetic acid-, magnesium sulphate- and kaolin-evoked writhing and formalin	GW9662 and PEA	PEA (20 $mg \cdot kg^{-1}$ per i.p.) GW9662 (2 $mg \cdot kg^{-1}$)	Intraperitoneal	Swiss CD1 mice and PPARα null type mice	PEA had antihyperalgesic effect on mechanical and thermal stimulus. Single intraperitoneal administration of GW9662 produced a reversion of analgesic effect of both compounds tested (butyrate and FBA).	Russo *et al.* (2016)
Inflammatory and visceral	Formalin and writhing	OEA **WY14643**	0.5, 1, 5, 10 and 20 $mg \cdot kg^{-1}$ (OEA)	Intraperitoneal	CD1 mice (wild type and PPARα null)	Treatment with OEA decreased the writhing response induced	Suardíaz *et al.* (2007)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
			5 and 20 mg·kg^{-1} (WY14643)			by acetic acid and formalin-evoked nociceptive behaviour (both phases) in both wild and KO mice. WY14643 did not affect the early phase of the formalin test whereas it slightly decreased the late phase.	
Neuropathic	Chronic constriction injury of sciatic nerve (CCI)	PEA	10 mg·kg^{-1}	Intraperitoneal	Murine	Administration of PEA reduced thermal hyperalgesia and mechanical allodynia; these effects were mediated by PPARγ.	Costa *et al.* (2008)
Neuropathic	Chronic constriction injury of sciatic nerve (CCI)	PEA	10 mg·kg^{-1}	Intraperitoneal for 7 days	C57BL/6J mice	Administration of PEA reduced thermal hyperalgesia and mechanical allodynia.	Bettoni *et al.* (2013)
Neuropathic	Spared nerve injury	15d-PGJ_2 and rosiglitazone (PPARγ agonists)	25, 50, 100 and 200 μg (15d-PGJ_2) amd 25, 50 and 100 μg (rosiglitazone)	Intrathecal	Sprague–Dawley rats	Treatments with the drugs (dose of 100 μg) decreased mechanical and cold hypersensitivity. Concomitant treatment with PPARγ antagonist (BADGE) reversed these effects.	Churi *et al.* (2008)
Neuropathic	Spared nerve injury	Pioglitazone (PPARγ agonist)	1, 3 and 10 mg·kg^{-1}·day^{-1} during 7 days (i.p.) 0, 0.3, 3.0, 30.0 mg·kg^{-1} daily during 7 days (included in the diet)	Intraperitoneal and oral	Sprague–Dawley RATS	Treatment with pioglitazone had anti-allodynic and anti-hyperalgesic effects, reversed by the PPARγ antagonist (GW9662).	Morgenweck *et al.* (2013)
Neuropathic	Spared nerve injury	Pioglitazone (PPARγ agonist)	2 and 10 mg·kg^{-1} (i.p.) and 0–300 μg (i.t.)	Intraperitoneal and intrathecal	Sprague–Dawley rats	Treatment rapidly reduced hyperalgesia induced by SNI; administration of GW9662 (PPARγ antagonist) reversed the effects.	Griggs *et al.* (2015)
Neuropathic	Diabetic-induced hyperalgesia	Pioglitazone (PPARγ agonist)	30 mg·kg^{-1}·day^{-1}	Oral (diet)	ZL and ZDF rats	Treatment reduced mechanical and thermal (hot and cold) hyperalgesia in diabetic rats.	Griggs *et al.* (2016)
Neuropathic	Silk suture thread of the sciatic nerve	Pioglitazone (PPARγ agonist)	1–25 mg·kg^{-1}	Oral (diet)	ICR mice	Treatment attenuated tactile allodynia.	Maeda *et al.* (2008)
Neuropathic	Partial sciatic nerve ligation	Rosiglitazone (PPARγ agonist)	3 and 10 mg·kg^{-1}	Intraperitoneal and local	C57BL6 mice	Systemic rosiglitazone treatment early in the course of progressive inflammation ameliorated tactile allodynia.	Takahashi *et al.* (2011)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Neuropathic	Diabetic-induced hyperalgesia	PEA	30 mg·kg^{-1}	Intraperitoneal	Mice	Treatment with PEA relieves mechanical allodynia.	Donvito *et al.* (2015)
Neuropathic	Paclitaxel-induced allodynia	PEA and GW6471 (PPARα antagonist)	30 mg·kg^{-1} (PEA) and 2 mg·kg^{-1} (GW6471)	Intraperitoneal, intraplantar, intrathecal and i.c.v.	ICR mice	PEA treatment had anti-allodynic effects and the treatment with GW6471 (PPARα antagonist) reversed these effects.	Donvito *et al.* (2016)
Neuropathic	Chronic constriction injury of sciatic nerve (CCI)	PEA	30 mg·kg^{-1}·day^{-1}	Subcutaneous (daily)	Wild-type and PPARα −/− (KO) C57BL6 mice	On day 14, PEA prevented pain threshold alterations in Randall–Selitto and Dynamic Plantar Aesthesiometer tests. In PPAR-α null mice PEA treatment failed to induce pain relief.	Di Cesare Mannelli *et al.* (2013)
Neuropathic	Spared nerve injury	PEA and OEA	10 mg·kg^{-1}·day^{-1} during 15 days (OEA and PEA) and 6 nmol per mouse (PEA and OEA)	Intraperitoneal and intra-mPFC	CD-1 mice	Repeated PEA and OEA treatments significantly increased both the thermal and mechanical thresholds in SNI mice. PEA microinjection decreased mechanical threshold with maximum effect at 75 min post-drug. OEA microinjections immediately and transiently reduced mechanical allodynia that lasted up to 30 min post-injection.	Guida *et al.* (2015)
Neuropathic	**Oxaliplatin**-induced neuropathy	PEA	30 mg·kg^{-1} (acute and chronic administration)	Intraperitoneal	Sprague–Dawley rats	Single administration of PEA was able to reduce oxaliplatin-dependent pain induced by mechanical and thermal stimuli. The repeated treatment with PEA prevented lowering of pain threshold as well as increased pain on suprathreshold stimulation.	Di Cesare Mannelli *et al.* (2015)
Neuropathic	Spinal cord injury	Pioglitazone	0.5, 1.5 or 3.0 mg·kg^{-1} (pioglitazone) and 2 mg·kg^{-1} (GW9662)	Intraperitoneal	Sprague–Dawley rats	Pioglitazone treatment significantly increased thermal threshold in spinal cord injured rats compared to the vehicle group. The administration of pioglitazone + GW9662 (PPARγ antagonist) or GW9662 alone did not result in significant differences to post-SCI surgery rats treated with vehicle.	Park *et al.* (2007)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Neuropathic	Diabetes-induced neuropathic pain	Pioglitazone	10 mg·kg^{-1}	Oral (chronic administration – 28 days)	Sprague–Dawley rats	The chronic administration of pioglitazone did not attenuate the hyperalgesia induced by the high fat diet/streptozotocin (HFD/STZ) model of diabetes.	Byrne *et al.* (2015)
Neuropathic	Sciatic nerve ligation (SNL)	Pioglitazone	4.5 and 9.0 mg·mg^{-1}	Intraperitoneal	Wistar rats	Both doses of pioglitazone attenuated hyperalgesia in the hot plate test and the cold allodynia effect of rats submitted to SNL.	Garg *et al.* (2017)
Neuropathic	Partial sciatic nerve ligation (PSL)	Pioglitazone	1, 5 or 25 mg·kg^{-1}	*Per os* (p.o.) during 5 days	ICR mice	Pioglitazone reduced the tactile allodynia at all doses. However, pioglitazone did not affect nociceptive responses in sham mice.	Iwai *et al.* (2008)
Neuropathic	Tibial and sural nerve transection (TSNT)	Rosiglitazone	2.5, 5 or 10 mg·kg^{-1}	*Per os* (p.o.) daily for 28 days	Wistar rats	Administration of rosiglitazone (at 5 and 10 mg·kg^{-1}) reduced the mechanical and cold hyperalgesia induced by TSNT without affecting heat hyperalgesia.	Jain *et al.* (2009)
Neuropathic	Lumbar 5 spinal nerve transection	Pioglitazone	2.5, 5 or 10 mg·kg^{-1}	*Per os* (p.o.) daily for 14 days	Sprague–Dawley rats	Pioglitazone (5 and 10 mg·kg^{-1}) attenuated mechanical hyperalgesia produced by lumbar 5 spinal nerve transection	Jia *et al.* (2010)
Neuropathic	Trigeminal inflammatory compression (TIC)	Pioglitazone, GW0742 (PPAR β/δ agonist), bezafibrate, fenofibrate, GW9662	100, 300 or 600 mg·kg^{-1} (pioglitazone); 1 or 6 mg·kg^{-1} (GW0742); 100 mg·kg^{-1} (bezafibrate); 200 mg·kg^{-1} (fenofibrate); 30 mg·kg^{-1} (GW9662)	Oral – pioglitazone 600 mg·kg^{-1} and bezafibrate 100 mg·kg^{-1} Intraperitoneal – all the others	C57BL/6 mice	Systemic administration of pioglitazone attenuates whisker pad mechanical allodynia at doses of 300 and 600 mg·kg^{-1}. Administration of GW9662 prior to pioglitazone (300 mg·kg^{-1}) blocked the analgesic effect of pioglitazone. GW0742 (6 mg·kg^{-1}) partially attenuated mechanical allodynia in mice with TIC injury compared to vehicle treated mice.	Lyons *et al.* (2017, 2018)
Neuropathic	Chronic constriction injury (CCI)	Pioglitazone	20 mg·kg^{-1}·day^{-1}	Oral – daily for 14 days	Sprague–Dawley rats	Pioglitazone attenuated the CCI-induced mechanical and thermal hyperalgesia.	Murad and Ayuob (2015)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Neuropathic	Spinal nerve ligation (SNL)	Pioglitazone	5, 10 or 20 mg·kg^{-1}	Intraperitoneal – daily for 28 days	Sprague–Dawley rats	Higher doses of pioglitazone attenuated the SNL-induced mechanical allodynia, cold allodynia, mechanical hyperalgesia and thermal hyperalgesia.	Pottabathini *et al.* (2016)
Neuropathic	Oxaliplatin-induced neuropathic pain	15 Thiazolidinones (TZDs) and GW9662	40 mg·kg^{-1} (TZDs) 4 mg·kg^{-1} (GW9662)	Intraperitoneal	C57BL/6 mice	Except for compound 14, all TZDs showed antinociceptive properties; these TZDs attenuated oxaliplatin-induced mechanical hyperalgesia. This effect was prevented by GW9662 (PPARγ antagonist).	Moreira *et al.* (2017)
Neuropathic	Sciatic nerve ligation	GW6471	5, 10 or 20 mg·kg^{-1}	Intraperitoneal	C57BL/6 wild-type and PPARα null lineages	Higher sensitivity to thermal and mechanical non-noxious and noxious stimuli, and cold and mechanical allodynia and heat hyperalgesia was observed in mice lacking PPARα. Writhing after acetic acid were also enhanced in mutant mice. The blockade of PPARα did not alter nociceptive behaviour.	Ruiz-Medina *et al.* (2012)
Neuropathic	Oxaliplatin-induced neuropathic pain	Rosiglitazone	3 and 10 mg·kg^{-1}	*Per os* (p.o.) daily for 20 days	Sprague–Dawley rats	Rosiglitazone attenuated hyperalgesia and allodynia resulted by oxaliplatin neuropathy.	Zanardelli *et al.* (2014)
Neuropathic	Trigeminal nerve injury (TNI)	Pioglitazone	100 mg·kg^{-1}	Intraperitoneally – daily for 7 days	C57BL/6 mice	DCS (NMDA agonist) and pioglitazone combination n attenuated orofacial neuropathic pain and anxiety related behaviours. The treatment with pioglitazone alone did not alter nociceptive behaviour.	Lyons *et al.* (2017, 2018)
Neuropathic	Peripheral nerve injury – L5 Spinal nerve transection	Pioglitazone and GW9662	10 mg·kg^{-1} (pioglitazone) 2 mg·kg^{-1} (GW9662)	Intraperitoneal	Sprague–Dawley rats	Pioglitazone improved the mechanical hyperalgesia in operated rats. This effect was reversed by GW9662.	Jia *et al.* (2013)
Neuropathic	Chronic constriction injury (CCI)	Pioglitazone and GW9662	10 mg·kg^{-1} (pioglitazone) 2 mg·kg^{-1} (GW9662)	Intraperitoneal	Sprague-Dawley rats	Treatment with pioglitazone attenuated CCI-induced hyperalgesia. This effect was reverrsed by GW9662 administration.	Jia *et al.* (2016)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Neuropathic and Visceral	Acetic acid induced visceral pain, sciatic nerve injury (SNI)	**MK886** (PPARα antagonist)	2 mg·kg^{-1}	Intraperitoneal	ICR mice, Kunming mice and C57BL/6J mice and PPAR-α knockout mice (−/−)	F96 (selective NAAA inhibitor) had an overall antinociceptive effect in the different models and tests carried out in the study. This effect was widely blocked by PPARα antagonist MK886 and by genetic disruption of PPAR-α.	Yang *et al*. (2015)
Visceral	Diarrhoea-predominant irritable bowel syndrome (D-IBS)	Pioglitazone and GW9662	2 mg·kg^{-1} (pioglitazone); 3 mg·kg^{-1} (GW9662)	Intraperitoneal on days 7, 9 and 11	Wistar rats	Pioglitazone reduced visceral hypersensitivity and defecation frequency and increased nociceptive thresholds.	Paragomi *et al*. (2014)
Other	–	PEA	3 and 6 nmol	Intra-vlPAG	Wistar rats	Reduced thermo-nociceptive threshold, as well as on/off cell activity in the rostro-ventromedial medulla (RVM).	De Novellis *et al*. (2012)
Other	–	Pioglitazone and GW9662 (PPARγ antagonist)	10 or 30 mg·kg^{-1} (pioglitazone) 2.5 or 5 mg·kg^{-1} (GW9662)	Oral (*via* gavage) – Daily (concomitant with morphine administration or for the prior 2 days before testing)	C57 mice	Treatment with pioglitazone attenuated the development of morphine tolerance. Pioglitazone administration in mice that were not chronically treated with morphine does not have an effect in nociception. Pretreatment with GW9662 reversed the effects of pioglitazone in morphine-treated rats. GW9662 alone does not have an effect in nociceptive responses. The development of tolerance for morphine is more pronounced in PPARγ knockout mice.	De Guglielmo *et al*. (2014)
Other	–	Pioglitazone and GW9662	20 or 40 mg·kg^{-1} (pioglitazone) 2 mg·kg^{-1} (GW9662)	*Per os* (p.o.) (pioglitazone) – daily for 17 days concomitant with morphine treatment Subcutaneous (GW9662)	Wistar rats	Treatment with pioglitazone attenuated the development of morphine tolerance. GW-9662 administration 30 min before pioglitazone antagonized the mentioned pioglitazone-induced effects.	Ghavimi *et al*. (2015)

continues

Table 2

(Continued)

Type of pain	Model	Drug	Dose	Route of administration	Animal	Outcome	Reference
Other	–	Pioglitazone and GW9662	5, 10, 20 or 40 mg·kg^{-1} (pioglitazone) 2 mg·kg^{-1} (GW9662)	*Per os* (p.o.) (pioglitazone) – daily for 17 days concomitant with morphine treatment Subcutaneous (GW9662) – daily before pioglitazone administration	Wistar Rats	The highest dose of pioglitazone *per se* did not alter the pain threshold in tail-flick test. Treatment with pioglitazone attenuated the development of morphine tolerance and GW-9662 administration 30 min before pioglitazone antagonized the pioglitazone-induced effects.	Ghavimi *et al.* (2014)
Other	Incisional pain	Rosiglitazone	25 μg	Intraplantar (in loci)	BKS.Cg − +Leprdb/ +Leprdb/Jcl Mice	Rosiglitazone alleviates mechanical hyperalgesia resulted by the incision.	Saito *et al.* (2016)
Other	Incisional pain	Rosiglitazone	0.5 mg·mL^{-1}	Local (intraplantar)	C57BL/6 mice	Local administration of rosiglitazone immediately after the procedure ameliorates thermal and mechanical hyperalgesia.	Hasegawa-Moriyama *et al.* (2012)

The Table was constructed based on searches within Pubmed central (https://www.ncbi.nlm.nih.gov/pmc/) and Google scholar (https://scholar.google.co.uk/) using combinations of one or more of the following search terms: PPARs, PPARα, PPARβ, PPARγ, PEA, OEA, synthetic PPAR ligands, pharmacological effects, CNS, brain, spinal cord, dorsal root ganglion, animal models and pain.

PPARα protein expression in the spinal cord has also been demonstrated in earlier studies (Benani *et al.*, 2004, Okine *et al.*, 2015). The functional relevance of PPARα signalling in the spinal cord to nociceptive processing is demonstrated at least in part by the reported increases in PPARα activation or protein expression in animal models of chronic inflammatory and neuropathic pain states. For example, using electrophoretic mobility shift assays (EMSA), Benani and colleagues were able to demonstrate a rapid increase in activation of the PPARα protein isoform in the rat spinal cord after injection of complete Freund's adjuvant into the hind paw (Benani *et al.*, 2004). Moreover, increased PPARα protein expression in the ipsilateral spinal cord was observed in the rat spinal nerve ligation model of neuropathic pain (Okine *et al.*, 2015). Furthermore, down-regulation of PPARα protein expression in the spinal cord contributed to augmented peripheral inflammation and inflammatory hyperalgesia in diet-induced obese rats (Wang *et al.*, 2014). While the pathophysiological relevance of PPARα activation or changes in PPARα protein expression in the spinal cord during hyperalgesia requires further investigation, these findings provide evidence for PPARα, as a potentially important player in spinal pain processing. In addition to PPARα, PPARγ is also expressed in the spinal cord (Table 1). Increased PPARγ protein expression in the spinal trigeminal caudalis 3 weeks after trigeminal nerve injury in mice has been reported to play a significant role in trigeminal nociceptive transmission, as demonstrated by the attenuation of whisker pad mechanical allodynia (Lyons *et al.*, 2017), and identifies PPARγ as a potential therapeutic target for orofacial neuropathic pain.

In comparison, there is a paucity of data on the expression or activation of PPARβ/δ in the spinal cord in inflammatory or neuropathic pain states. In this regard, further characterization of PPARβ/δ is essential to establish whether changes in expression or endogenous activation of the receptor occur in pain states, and the extent to which they contribute to spinal pain processing.

As shown in Table 1, all three PPAR isoforms are widely expressed supraspinally, in key brain regions involved in pain processing. The expression of PPARs at key relay sites such as the thalamus and the midbrain periaqueductal grey (PAG) may reflect a role for PPAR signalling in modulating the activity of ascending and descending pain pathways. Furthermore, the presence of PPARs within cortical regions and the amygdala suggests potential involvement of PPAR signalling in modulating cognitive or affective components of pain. While there is currently no direct evidence in support of this hypothesis, this view is however consistent with the role of both the cortex and amygdala as key brain regions involved in the modulation of the cognitive-affective components of pain (see Fuchs *et al.*, 2014; Neugebauer, 2015).

Evidence from pharmacological or genetic manipulation studies for a role of PPARs in pain

Pharmacological or genetic manipulation of PPARα and PPARγ using selective agonists, antagonists or gene knockout approaches specifically targeting these receptors within the pain pathway has been shown to alter nociceptive processing, demonstrated by changes in neuronal activity or behavioural responses in animal models of inflammatory and neuropathic pain (Figure 1). Both PPARα and PPARγ regulate the release of pro-inflammatory mediators associated with tissue or nerve injury through the inhibition of pro-inflammatory signalling pathways such as NF-κB activation (Cuzzocrea *et al.*, 2008, Delerive *et al.*, 2000) and suppression of downstream pro-inflammatory molecules including COX-2 and iNOS (D'Agostino *et al.*, 2009), two key players in the development of chronic pain states. The majority of pharmacological studies to date demonstrate antinociceptive effects of both endogenous and synthetic agonists of PPARα and PPARγ in animal models of inflammatory and neuropathic pain (for a comprehensive summary of the published studies to date see, Table 2). It is pertinent to note that a significant proportion of preclinical studies investigating the role of endogenous PPAR ligands in nociceptive processing in the periphery and the CNS have mainly focused on the effects of PEA, with relatively little attention given to the role of OEA. One possible reason that may account for this apparent bias is the reported activation of **TRPV1** pronociceptive non-selective cation channels (the vanilloid receptors), by OEA (Ahern, 2003). Thus, it is possible that any PPAR-mediated analgesic effects of OEA are likely to be nullified by its TRPV1-mediated pronociceptive effects, as demonstrated in an animal model of neuropathic pain (Guida *et al.*, 2015).

The pharmacological effects of PEA involve both transcription-dependent and transcription-independent or non-genomic mechanisms. While the former account primarily for the anti-inflammatory effects associated with PPAR activation, the non-genomic mechanisms are thought to underlie the rapid antinociceptive effects of not only PEA but also other synthetic PPAR agonists in animal models of inflammatory and neuropathic pain (Churi *et al.*, 2008, LoVerme *et al.*, 2006; Donvito *et al.*, 2015). It is, however, important to note that the non-genomic mechanisms mediating the effects of PEA are not independent of PPAR expression or activation. Indeed, evidence from studies with PPAR knockout mice suggests that the modulation of medium and large **Ca^{2+} channels** associated with the rapid antinociceptive effects of PEA and other synthetic PPARα agonists on inflammatory pain behaviour in mice are contingent upon PPARα receptor expression in the DRG (LoVerme *et al.*, 2006). Given that these rapid antinociceptive effects are incompatible with the duration of longer term transcription-dependent mechanisms, the modulation of Ca^{2+} channels in this instance may be a by-product of protein–protein interactions induced by changes in PPAR protein conformation following the binding of agonist to the receptor. Further studies aimed at identifying the precise mechanisms involved could potentially lead to the identification of novel therapeutic targets for the treatment of pain.

The non-genomic effects of PEA may also involve the indirect activation of other receptors, such as cannabinoid receptors, mediated by anandamide (**AEA**) through the so-called 'entourage hypothesis' (LoVerme *et al.*, 2005). In this context, competition by PEA for fatty acid amide hydrolase (**FAAH**)-mediated hydrolysis, is thought to provide a

'sparing effect' on AEA hydrolysis by FAAH, resulting in enhanced signalling at endocannabinoid targets, in particular **CB_1** or **CB_2** receptors, to produce analgesia (Tuo *et al.*, 2017). In keeping with this, we have recently demonstrated a role for CB_1 receptors in the antinociceptive effects of PEA injected directly into the anterior cingulate cortex (ACC) in the rat formalin test (Okine *et al.*, 2016). Moreover, given the preferential binding of AEA over PEA to PPARγ (Bouaboula *et al.*, 2005), it is possible that entourage-mediated signalling involving AEA is likely to underpin the PPARγ-mediated antinociceptive effects of PEA (Costa *et al.*, 2008). Indeed, AEA binds to and activates PPARα in addition to PPARγ (O'Sullivan and Kendall, 2010). Here, it is important to note that these findings have implications not only for the interpretation of data demonstrating the analgesic effects of endogenous PPAR ligands such as PEA and OEA or inhibitors of FAAH which enhance levels of endogenous PPAR agonists but also the design of such experiments given the possible involvement of other receptor systems other than PPARs. In this regard, the inclusion of appropriate robust control experiments involving PPAR antagonists or gene knockout should always be considered when examining a role for PPARs as mediators of the pharmacological effects of endogenous PPAR ligands.

The analgesic effects of PPAR agonists may also be mediated *via* modulation of cellular organelles. For example, a combination drug therapy of the synthetic PPARγ agonist **pioglitazone** with **D-cycloserine** attenuates chronic orofacial neuropathic pain and associated anxiety by improving mitochondrial function following trigeminal nerve injury (Lyons *et al.*, 2018). With the molecular mechanisms continuing to be elucidated, these findings widen the scope and increase the appeal of PPAR agonists as therapeutic agents for treating pain. Furthermore, given the involvement of both genomic and non-genomic mechanisms in mediating the effects of PPAR agonists, further studies aimed at determining which mechanisms are predominant in different types of pain will be important for the optimization of the analgesic effects of PPAR agonists.

It is however important to note that while the weight of evidence is in favour of antinociceptive effects of PPARα or PPARγ activation at multiple sites within the pain pathway, recent findings from our group also reveal a pain permissive or facilitatory role for PPAR signalling in discrete brain regions such as the ACC (Okine *et al.*, 2017, Okine *et al.*, 2014). Intra-ACC injection of **GW6471** (selective PPARα antagonist) or **GW9662** (selective PPARγ antagonist) significantly suppressed the onset of formalin-evoked nociceptive behaviour in rats (Okine *et al.*, 2017). Such permissive or facilitatory roles of endogenous PPAR activation within the ACC may allow the animal to perceive pain and take the necessary actions to escape from, or avoid injury.

The specific role of PPARβ/δ activation in pain processing remains largely unknown, despite molecular evidence demonstrating the presence of the receptor at key sites within the pain pathway such as the spinal cord, thalamus and PAG (Table 1; Figure 1). However, in a previous study, administration of **GW0742**, a selective PPARβ/δ receptor agonist (0.1 $mg{\cdot}kg^{-1}$ per i.p. for 4 days) significantly decreased mechanical and thermal hyperalgesia in adult male Wistar rats, induced by carrageenan injection into the hind paw, compared with vehicle-treated controls. These effects were reversed in the presence of the selective PPAR β/δ antagonist **GSK0660** (0.3 $mg{\cdot}kg^{-1}$ per i.p. for 4 days) (Gill *et al.*, 2013). These findings demonstrate the potential of PPAR β/δ agonists as therapeutic agents for the treatment pain. Further preclinical studies are however needed to understand fully the extent to which PPARβ/δ-mediated signalling modulates nociceptive transmission within the CNS.

Evidence from clinical trials

Over the last couple of decades, the analgesic effects of PEA, an endogenous PPAR agonist, or its derivatives, have been demonstrated in several clinical trials in different pain conditions. In a recent comprehensive review of 21 clinical trials, Gabrielsson *et al.*, reported that oral or sublingual treatment with PEA or micronized PEA (PEA-μm; reduced crystal particles of PEA that enhance the dissolution and reduce the absorption variability) reduced pain intensity in patients with neuropathic and inflammatory joint pain phenotypes (Gabrielsson *et al.*, 2016). Significantly, these treatments were not associated with any marked side effects. Similar reports of the analgesic effects of PEA in clinical trials have been discussed in another comprehensive review by Hesselink and Hekker (2012). These studies report that administration of PEA (doses ranging from 300 to 600 $mg{\cdot}day^{-1}$; mostly orally administered as tablets) is effective against a range of pain conditions including neuropathic pain, low back pain and postoperative pain.

In contrast, Andresen and colleagues report that a 12-week treatment with PEA-μm did not alleviate pain in patients with spinal cord injury-induced neuropathic pain, compared to placebo-treated patients (Andresen *et al.*, 2016). The authors however point out that the limited knowledge on PEA-μm pharmacokinetics, including information on diffusion to the CSF, make it difficult to draw more specific conclusions. It is also possible that the heterogeneity in the population of spinal cord injury pain phenotypes could have affected the outcome of this study. These clinical effects of PEA however, while suggestive of a role for PPAR signalling, do not necessarily rule out the involvement of other receptor systems, given the multiple signalling pathways mediating the pharmacological effects of PEA as demonstrated in preclinical studies and discussed elsewhere in this review. In this regard, the use of synthetic PPAR agonists in clinical trials may be more beneficial and informative. In keeping with this line of argument, a more defined role for PPAR signalling in modulating human pain conditions was demonstrated in a study by Smith and colleagues, who reported a reduction in occurrence of myalgia, a muscoskeletal pain disorder, in men receiving **clofibrate**, an approved PPARα agonist used clinically for the treatment of dyslipidemia (Smith *et al.*, 1970). However, subsequent attempts at replicating these early promising results using other fibrates to alleviate muscular pain have not been successful (Biga *et al.*, 2005). Nevertheless, these drugs were found to be effective in attenuating pain associated with rheumatoid arthritis and osteoarthritic pain (van Eekeren *et al.*, 2013). These findings indicate that synthetic PPARα agonists can have analgesic effects in specific types of pain.

Synthetic agonists of PPARγ are currently used clinically as insulin sensitizers in the treatment of non-insulin dependent (Type 2) diabetes. However, despite preclinical evidence demonstrating their analgesic effects in a variety of animal models of inflammatory and neuropathic pain (see Table 2), to our knowledge, there are currently no published clinical studies investigating their effects on pain in human subjects or patients. Similarly, there is a paucity of clinical studies investigating the effects of synthetic PPARβ agonists on pain.

A potential role for PPAR signalling in interactions between pain and negative affect

The close relationship between stress (and stress-related disorders such as anxiety and depression) and chronic pain is now widely recognized (Jennings *et al.*, 2014, Olango and Finn, 2014). Although the role of PPAR signalling in the modulation of stress-pain interactions remains largely unexplored, the abundant expression of PPARs in key brain regions involved in the modulation of the cognitive and affective components of pain such as the amygdala and PAG (Table 1 and Figure 1), and the availability of endogenous PPAR ligands in these brain structures, supports a potential role for the PPAR signalling system in stress–pain interactions and as a potential therapeutic target for the treatment of comorbid chronic pain and affective disorders. This view is also consistent with our recent demonstrations of enhanced second phase formalin-evoked nociceptive behaviour following selective blockade of PPARγ in the lateral PAG in Wistar-Kyoto (WKY) but not Sprague–Dawley (SD) rats (Okine *et al.*, 2017). The WKY rat strain is stress-hyperresponsive and exhibits a hyperalgesic phenotype to nociceptive stimuli compared with SD rats and is considered a suitable genetic model for studying stress–pain interactions (Burke *et al.*, 2010, Rea *et al.*, 2014, O'Mahony *et al.*, 2013). While the specific contribution of PPARγ signalling to the stress hyperresponsive phenotype of WKY rats is currently not clear, the differential effects of pharmacological modulation of PPARγ in the lateral PAG on formalin-evoked nociceptive behaviour in SD and WKY rats suggests an important role for this receptor in a genetic background that is prone to stress and hypersensitivity to nociceptive stimuli. These findings also suggest that PPARγ-mediated signalling in the lateral PAG may represent a potential therapeutic target for future development of effective therapies for treating comorbid chronic pain and stress-related disorders such as anxiety and depression. The therapeutic potential of PPARγ for treatment of pain and mood disorder comorbidity is also supported by evidence that pioglitazone attenuates chronic constriction injury (CCI)-induced depression-related behaviour in the forced swim test in rats (Garg *et al.*, 2017)), reduces anxiety-like behaviour in a mouse model of chronic orofacial neuropathic pain (Lyons *et al.*, 2018) and augments both the anti-depressant and the antinociceptive effects of **fluoxetine** in the rat CCI model of neuropathic pain (Murad and Ayuob, 2015). Additional studies on the therapeutic potential of PPAR agonists (including those for PPARα and PPARβ/δ) for treatment of the affective/emotional component of chronic pain are warranted.

Future perspectives

Synthetic PPARα and PPARγ agonists such as clofibrate and **rosiglitazone**, respectively, are currently available clinically for the treatment of medical conditions such as dyslipidemia and non-insulin dependent (Type 2) diabetes, the latter of which is often associated with altered sensory processing in the extremities. The current clinical use of these drugs provides an opportunity for clinical trials to explore and evaluate their potential as novel analgesics for the treatment of intractable chronic pain conditions such as diabetic neuropathy.

It is however important to note that the development of analgesics targeting the PPAR signalling system must also take into account their potential adverse side effects

Table 3

Summary of adverse effects associated with PPAR activation

Cardiovascular effects	• Increased risk of myocardial infarction[a,b,c]
Tumorigenic effects	• Increased risk of bladder cancer in patients on long-term therapy with synthetic PPAR agonists[c,d] • Haemangioma and renal pelvic tumours[d]
Others peripheral effects	• PPAR agonist induced peripheral oedema formation *via* fluid retention[e,f] • Increased liver toxicity[g] • Inhibition of gastrointestinal motility[h] • Inhibition of human aortic smooth-muscle contraction associated with PPARα activation[i]

[a](Nissen and Wolski, 2007).
[b](Loke *et al.*, 2011).
[c](Friedland *et al.*, 2012).
[d](Aoki, 2007).
[e](Sunder Mudaliar *et al.*, 2003).
[f](Bełtowski *et al.*, 2013).
[g](Floyd *et al.*, 2009).
[h](Capasso *et al.*, 2001).
[i](Staels *et al.*, 1998).

(Table 3), given the important physiological roles of the PPAR signalling system. For example, the inhibitory effects of PEA on gastrointestinal motility (Capasso *et al.*, 2001) or on contraction of human aortic smooth muscle, associated with PPARα activation (Staels *et al.*, 1998,) may limit the therapeutic efficacy of PPAR-targeting analgesics. Nonetheless, evidence from clinical studies using PEA so far suggests that these side effects are unlikely to be of major concern over a short duration of administration of PPAR agonist and that the therapeutic benefits may outweigh the side effects. Moreover, the demonstration of cardioprotective and anti-tumour effects (Wright *et al.*, 2014) of some synthetic PPAR agonists, but not others, suggests that these reported adverse side effects may be agonist-dependent rather than PPAR target-dependent. Further studies are however required to determine the long-term effects of persistent pharmacological modulation of PPAR signalling in chronic pain states.

The role of PPAR signalling in the development or modulation of other chronic pain conditions, such as osteoarthritis, cancer pain and migraine requires further study, as does the interaction of PPAR signalling with other well-characterized endogenous pain control systems and currently prescribed analgesics. On this latter point, the PPARγ agonist pioglitazone has been shown to attenuate tolerance to **morphine** in a rat model of inflammatory pain (Ghavimi *et al.*, 2015, Ghavimi *et al.*, 2014) and in the mouse tail immersion test (de Guglielmo *et al.*, 2014). Similar potential synergistic antinociceptive interactions with the cannabinoid (Russo *et al.*, 2007) and TRPV1 (Ambrosino *et al.*, 2014) signalling systems have been reported. In respect of the latter study, the evidence suggests that the potential antinociceptive effects of this synergistic interaction are likely to be facilitated by PPARα-dependent activation of TRPV1 channels and subsequent desensitization of the receptor. Elsewhere, a synergistic antinociceptive interaction between PEA and the opiate drug, **tramadol**, has been demonstrated in the mouse formalin test (Déciga-Campos *et al.*, 2015). The antinociceptive mechanisms of the PEA and tramadol combination involved the opioid receptor, TRPV1 and PPARα. Significantly, the sedative effects of the combination of PEA and tramadol were minimal compared with those observed with individual treatments. Collectively, these findings make a compelling case for an increased understanding of PPAR signalling and its crosstalk with other analgesic targets. Such knowledge could lead to the development of novel PPAR signalling based-analgesic strategies.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c).

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Conflict of interest

The authors declare no conflicts of interest.

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