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Functional interactions between cannabinoids, omega-3 fatty acids, and peroxisome proliferator-activated receptors: Implications for mental health pharmacotherapies

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Abstract

Cannabis contains a plethora of phytochemical constituents with diverse neurobiological effects. Cannabidiol (CBD) is the main non-psychotropic component found in cannabis that is capable of modulating mesocorticolimbic DA transmission and may possess therapeutic potential for several neuropsychiatric disorders. Emerging evidence also suggests that, similar to CBD, omega-3 polyunsaturated fatty acids may regulate DA transmission and possess therapeutic potential for similar neuropsychiatric disorders. Although progress has been made to elucidate the mechanisms underlying the therapeutic properties of CBD and omega-3s, it remains unclear through which receptor mechanisms they may produce their purported effects. Peroxisome proliferator-activated receptors are a group of nuclear transcription factors with multiple isoforms. PPARγ is an isoform activated by both CBD and omega-3, whereas the PPARα isoform is activated by omega-3. Interestingly, the activation of PPARγ and PPARα with selective agonists has been shown to decrease mesocorticolimbic DA activity and block neuropsychiatric symptoms similar to CBD and omega-3s, raising the possibility that CBD and omega-3s produce their effects through PPAR signaling. This review will examine the relationship between CBD, omega-3s, and PPARs and how they may be implicated in the modulation of mesocorticolimbic DAergic abnormalities and associated neuropsychiatric symptoms.

KEYWORDS

cannabinoids, dopamine, GABA, nucleus accumbens, omega-3 fatty acids, PPAR, prefrontal

Abbreviations: 2-AG, 2-arachidonoyl glycerol; 5-HT1A, serotonin 5-HT 1A receptor subtype; AA, arachidonic acid; AEA, anandamide; Akt, protein kinase B; ALA, alpha-linolenic acid; AMPH, amphetamine; CB1, Cannabinoid Type 1 receptor; CBD, cannabidiol; DA, dopamine; DHA, docosahexaenoic acid; DHEA, docosahexaenoyl ethanolamine; EPA, eicosapentaenoic acid; EPEA, eicosapentaenoyl ethanolamine; GABA, gamma-amino-butyric acid; GSK-3, glycogen

synthase kinase-3; LA, linolenic acid; MAM, methylazoxymethanol acetate; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NAc, nucleus accumbens; NMDAR, *N*-methyl- d-aspartic acid receptor; OEA, oleoylethanolamide; P70s6K, ribosomal protein S6 kinase beta-1; PEA, palmitoylethanolamide; PPAR, peroxisome proliferator-activated receptor; PPI, prepulse inhibition; PUFA, long-chain polyunsaturated fatty acids; PV, parvalbumin; RMTg, rostromedial tegmental nucleus; THC, delta-9-tetrahydrocannabinol; VTA, ventral tegmental area.

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1 | CANNABINOID MODULATION OF MESOCORTICOLIMBIC FUNCTION: IMPLICATIONS FOR MENTAL HEALTH

The endocannabinoid system functions as a critical neuromodulatory system for various neurobiological processes such as the development of the central nervous system, synaptic plasticity (Lu & Mackie, 2016), emotion, and motivation (Marco et al., 2011; Rodriguez de Fonseca et al., 2004). In the brain, endogenous cannabinoids (endocannabinoids) mediate their effects primarily through the cannabinoid receptor-1 (CB1) (Garcia et al., 2016; Lu & Mackie, 2016). Signaling through the CB1 receptor system has been shown to critically modulate the activity states of neurons and neurotransmitter release within the mesocorticolimbic circuitry (Dazzi et al., 2014; Egerton et al., 2006; Gessa et al., 1998; Hajós et al., 2008; Melis et al., 2004; Oleson et al., 2012). In addition, both clinical and preclinical research have demonstrated critical interactions between cannabinoid signaling and modulation of neuropsychiatric symptoms via direct, functional interactions between these systems (Colizzi et al., 2019; Hajós et al., 2008; Loureiro et al., 2016). In particular, the endocannabinoid system potently modulates the mesolimbic dopamine (DA) system (Parsons & Hurd, 2015), which is composed of DAergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Russo & Nestler, 2013). CB1 receptors directly control VTA neuronal activity states (French et al., 1997) and modulate DA release (Cheer et al., 2004). In addition, CB1 signaling within the NAc can strongly regulate VTA DA activity through its modulation of inhibitory GABAergic signaling within the VTA (Fitoussi et al., 2018). The dysregulation of this system is implicated in various neurological processes and neuropsychiatric disorders such as addiction, anxiety, and schizophrenia (Alcaro et al., 2007; Zarrindast & Khakpai, 2015).

Beyond the endocannabinoid system, cannabis-derived phytocannabinoids, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been shown to strongly modulate the brain's mesocorticolimbic circuitry (Fitoussi et al., 2018; Norris et al., 2016; Renard, et al., 2016, 2017) and also modulate mental health-related symptoms (Englund et al., 2013; Leweke et al., 2012; Long et al., 2006; Martin-Santos et al., 2012; Moreira & Guimarães, 2005; Renard et al., 2017). THC, the main psychotropic component of cannabis, possesses dependence-producing properties (Prud'homme et al., 2015) and can induce anxiety and schizophrenia-like behavior (Niesink & van Laar, 2013; Renard, et al., 2017). Through the activation of CB1 receptors, THC strongly modulates endocannabinoid signaling (Parsons & Hurd, 2015) and can induce hyperactive DAergic states (Fitoussi et al., 2018; Renard, et al., 2017). It is believed that this dysregulation of VTA DA activity is responsible for the psychoactive and neuropsychiatric side-effects of THC (Bloomfield et al., 2016). Interestingly, cannabis also contains cannabidiol (CBD), a non-psychoactive compound that produces the opposite effects of THC (Renard, et al., 2017). For example, CBD up-regulates specific molecular pathways associated with neuropsychiatric disorders, in a manner opposite to THC (Renard, et al., 2016, 2017). In addition, CBD has been shown to decrease the activity of mesocorticolimbic DAergic activity states (Norris et al., 2016; Renard, et al., 2016). Thus, CBD may possess therapeutic potential for various neuropsychiatric disorders, including addiction, anxiety, and schizophrenia (Campos et al., 2013; Prud'homme et al., 2015; Zuardi et al., 2012). While considerable evidence has implicated CBD and associated neuropharmacological substrates (such as the 5-HT1A receptor) as important for the functional effects of CBD on the mesocorticolimbic system (Norris et al., 2016), critical questions remain concerning the precise molecular mechanisms that may underlie the potential therapeutic effects of CBD. Indeed, considerable evidence has demonstrated that CBD can interact with intracellular molecular substrates beyond the monoamine receptors (Esposito et al., 2011; Granja et al., 2012; O'Sullivan et al., 2009; Scuderi et al., 2014).

Importantly, emerging evidence is demonstrating the importance of dietary factors, including the omega-3–6 fatty acids and their downstream nuclear receptor targets, such as the peroxisome-proliferator activator receptor (PPARs) class, not only as important molecular targets for the actions of intrinsic and extrinsic cannabinoids (Dyall, 2017; Edwards & O'Flaherty, 2008; Esposito et al., 2011; Granja et al., 2012; Larrieu et al., 2012; Naughton et al., 2013; O'Sullivan et al., 2009; Scuderi et al., 2014), but as important modulators of neuropsychiatric symptoms (Amminger et al., 2010, 2015; Domi et al., 2016; Ferguson et al., 2014; Foll et al., 2013; McNamara et al., 2007; Rolland et al., 2012; Su et al., 2015; Yamada et al., 2014; Zimmer et al., 2002) and etiology (De Guglielmo et al., 2015; Melis et al., 2008, 2010; Panlilio et al., 2012; Zimmer et al., 2000). In this review, we will describe recent research highlighting how functional interactions between CBD, omega-3/6 fatty acids, and the PPAR nuclear receptor system might synergistically interact within the mesocorticolimbic system to modulate mental health-related phenomena.

2 | THE INTERPLAY BETWEEN OMEGA-3/6 FATTY ACIDS, ENDOCANNABINOIDS, AND NEUROPSYCHIATRIC PATHOLOGY

Long-chain polyunsaturated fatty acids (PUFAs) are essential human nutrients and consist of two major groups: omega-6 and omega-3 PUFAs (Yamada et al., 2014). Emerging evidence is

revealing critical roles for these fatty acids both in the neurometabolism of endocannabinoids and the regulation of CB1R signaling (Larrieu et al., 2012; Naughton et al., 2013; Dyall, 2017). Normal functional interactions between the omega-6/3 PUFAs and the endocannabinoid system require the presence of their precursor forms, linolenic acid (LA; omega-6), and alpha-linolenic acid (ALA; omega-3), respectively (Larrieu et al., 2012). LA is metabolized into arachidonic acid (AA) which is further processed into the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) (Larrieu et al., 2012) that are both agonists of the CB1R (Naughton et al., 2013). ALA is converted into the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and produces the endocannabinoids docosahexaenoyl ethanolamine (DHEA) and eicosapentaenoyl ethanolamine (EPEA) (Dyall, 2017), respectively. Interestingly, DHEA and EPEA are also CB1 agonists (Brown et al., 2010). However, DHEA, which is produced from DHA that is 250–300 times more prevalent than EPA in the brain (Dyall, 2015), has a significantly weaker affinity to cannabinoid receptors compared to AEA (Kim & Spector, 2013, 2018; Kim et al., 2016).

How does dietary exposure to omega-3 modulate brain levels of endocannabinoids? Previous research has shown that dietary supplementation with the omega-3, DHA, and EPA, enhances brain levels of omega-3 derived endocannabinoids such as DHEA but decreases omega-6 derived endocannabinoids such as AEA and 2-AG (Dyall, 2017). This evidence suggests that the derivation of DHEA and EPEA share the same biological pathways as AEA and 2-AG derivation. This is important in the function of the endocannabinoid system as it suggests that an omega-3 deficient diet may increase the generation of naturally occurring AEA and 2-AG and subsequently amplify CB1 activation. Given the known ability of both acute and chronic exposure to CB1R agonists, such as THC or synthetic agonists such as WIN-55 212–2 to activate mesocorticolimbic DAergic activity states (Fitoussi et al., 2018; French, 1997; French et al., 1997; Renard, et al., 2017)', this raises the possibility that the increase in AEA and 2-AG levels may similarly increase tonic DA activity states and dysregulate mesolimbic transmission. In support of this, omega-3-deficient diets appear to increase mesolimbic DA activity (Zimmer et al., 2002) and are linked to anxiety disorders (Su et al., 2015; Yamada et al., 2014), schizophrenia (McNamara et al., 2007), and addiction liability (Rabinovitz, 2014; Scaglia et al., 2016). In addition, a recent clinical trial has demonstrated that omega-3 dietary supplementation is capable of reducing conversion to psychosis in patients at high risk for schizophrenia and that relatively brief exposure to omega-3 PUFAs was sufficient to significantly reduce neuropsychiatric morbidity for up to 6 years post exposure (Amminger et al., 2010, 2015). Altogether, this evidence suggests that increased omega-3 levels may serve to normalize abnormal, pathological states of DAergic signaling, similar to effects observed with CBD administration (Renard, et al., 2016). However, the precise neuropharmacological and/or molecular signaling mechanisms implicated in the therapeutic properties of omega-3 are largely unknown (Dyall & Michael-Titus, 2008).

3 | PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS AND THE ENDOCANNABINOID SYSTEM

Peroxisome proliferator-activated receptors (PPAR) are a group of nuclear transcription factors that includes three isoforms: PPARα, PPARβ/δ, and PPARγ (O'Sullivan, 2016), distributed widely throughout the brain and body in various organ systems. PPARs form heterodimer complexes with retinoid-X receptors and then bind to select DNA sequences to influence the transcription of various cellular products. Most critically, the PPARs are known to regulate lipid and glucose metabolism and serve neuroprotective functions as well as mediating anti-inflammatory effects throughout the body and brain (Figure 1). Interestingly, different PPAR isoforms are activated by specific endocannabinoids, phytocannabinoids, and synthetic cannabinoids (O'Sullivan, 2016). Specifically, cannabinoid activation of PPARα and PPARγ has been implicated in the modulation of neuronal activity states (O'Sullivan, 2016). Interestingly, both PPARα and PPARγ receptor activation attenuates VTA DA activity (De Guglielmo et al., 2015; Melis et al., 2008, 2010; Panlilio et al., 2012) and demonstrates therapeutic potential for various neuropsychiatric disorders (Domi et al., 2016; Ferguson et al., 2014; Foll et al., 2013; Rolland et al., 2012). For example, PPARγ receptor activation shows potential for the treatment of various drug dependencies. As such, in preclinical studies, PPARγ agonists were shown to decrease alcohol consumption (Stopponi et al., 2011, 2013), heroin self-administration (De Guglielmo et al., 2015), opioid withdrawal, and susceptibility to opioid relapse (de Guglielmo et al., 2017). Preclinical trials have also shown that PPARγ signaling inhibits anxiety, whereas PPARγ deletion augments anxiety (Domi et al., 2016). In clinical trials, treatment with PPARγ agonists decreased cravings for cocaine in people with cocaine use disorder (Schmitz et al., 2017) and nicotine in frequent smokers (Jones et al., 2017). In addition, a preclinical study by Domi et al. (2019) demonstrated that activation of PPARγ directly in the amgydala or hippocampus could mitigate the expression of physical and affective nicotine withdrawal symptoms in mice. Similarly, a preclinical study reported that treatment with PPARα agonists decreases self-administration of nicotine and prevents relapse (Foll et al., 2013).

PPARα agonist treatment also demonstrates the therapeutic potential for schizophrenia (Rolland et al., 2012). For example, individuals with schizophrenia display defi- cits in prepulse inhibition (PPI), a form of sensorimotor

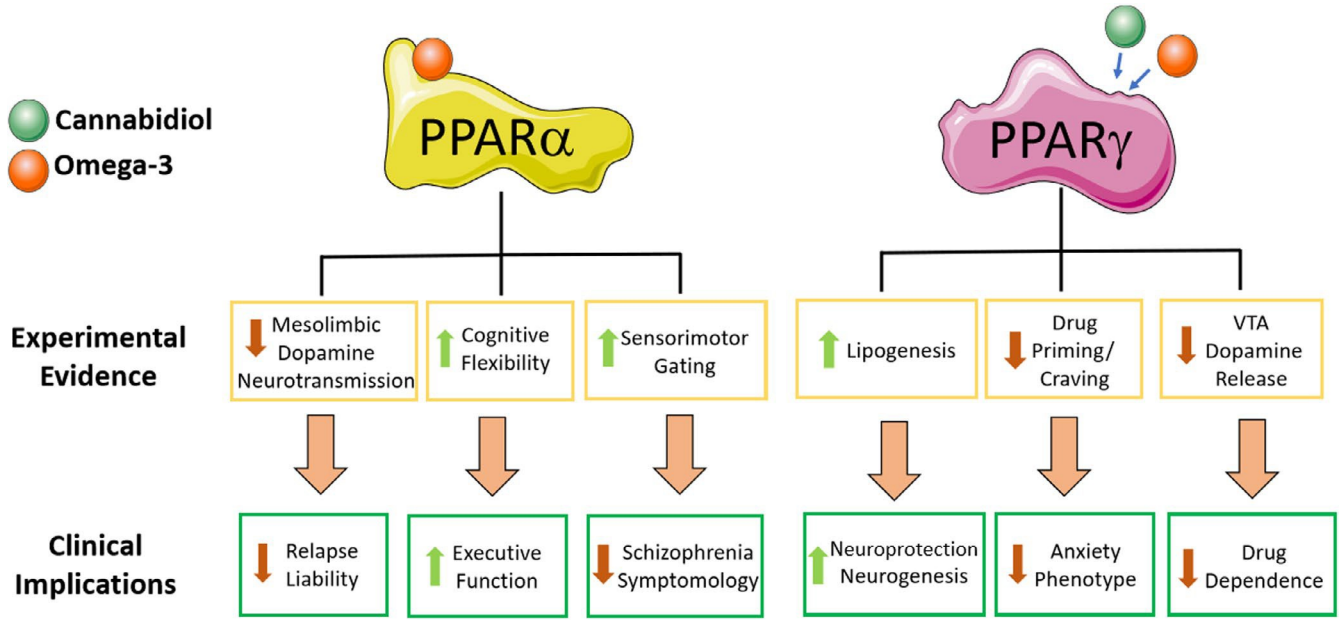

FIGURE 1 A schematic summary of several major downstream neurobiological actions of PPARα and PPARγ agonists and reported clinical implications. PPARα: peroxisome proliferator-activated receptor alpha; PPARγ: peroxisome proliferator-activated receptor gamma; VTA: ventral tegmental area

gating whereby the presentation of a prior weak stimulus (prepulse) inhibits a startle response to a stronger stimulus (pulse) (Powell et al., 2011). Rolland et al. (2012) reported that PPARα agonist administration was able to prevent PPI deficits in a preclinical neurodevelopmental model of schizophrenia, suggesting that PPARα targets may mediate sensory gating deficits present in the disorder.

Interestingly, both CBD and omega-3 fatty acids can activate PPARγ (Edwards & O'Flaherty, 2008; Esposito et al., 2011; Granja et al., 2012; O'Sullivan et al., 2009; Scuderi et al., 2014) which raises the possibility that CBD and omega-3 may produce their therapeutic effects through this receptor system. Omega-3s are also activators of PPARα (Grygiel-Górniak, 2014) although there is currently limited evidence to explain its functional interactions with phytocan- nabinoids (O'Sullivan, 2016). This raises the intriguing pos- sibility that PPAR signaling may be a nuclear convergence point for the therapeutic effects of both CBD and Omega-3 fatty acids. Emerging evidence (described below) is now demonstrating that these functional interactions may serve a modulatory role on mesocorticolimbic function and associ- ated neuropsychiatric syndromes.

4 | PPAR AND CANNABINOID MODULATION OF THE VENTRAL TEGMENTAL AREA

Numerous preclinical studies have demonstrated the abil- ity of THC to excite VTA DAergic neurons. Using in vivo extracellular recordings, French et al. (1997) reported that systemic THC induced dose-dependent excitations in VTA DA firing and bursting rates. The same effect was reported using WIN55 212-2 (French et al., 1997), a synthetic cannabimimetic CB1 agonist. A subsequent study by French found that the excitatory effects of THC and WIN55 212-2 were blocked by systemic pretreatments with the selective CB1R antagonist SR141716A which suggests that these effects are CB1R mediated. Interestingly, this group did not find an effect of systemic CBD administration on VTA DA activity.

Considerable evidence reports that activation of both PPARα (Melis et al., 2008, 2010; Panlilio et al., 2012) and PPARγ (De Guglielmo et al., 2015) attenuates VTA DA neuron activity. For example, using in vivo and in vitro electrophysiological recordings, Melis et al. (2008) re- ported that the endogenous PPARα agonists, oleoyletha- nolamide (OEA), and palmitoylethanolamide (PEA) block nicotine-induced excitation of VTA DA neurons (Melis et al., 2008). A subsequent study by Melis et al. (2010) re- ported that OEA decreases basal VTA DA activity, whereas the PPARα antagonist MK886 blocks this effect and ampli- fies basal VTA DA activity when applied alone in in vitro electrophysiology. With in vivo electrophysiology, the same study also found that the PPARα agonist WY14643 diminished the number of spontaneously active VTA DA neurons (Melis et al., 2010). In a different study, Panlilio et al. (2012) reported that intraperitoneal pretreatment with clofibrate, a PPARα agonist, suppressed the amplification of VTA DA activity by nicotine. In addition, clofibrate was able to reduce nicotine self-administration in animals and blocked the effects of nicotine re-exposure that in- duce relapse to nicotine (Panlilio et al., 2012). The effects

of clofibrate were blocked by the addition of MK886, a PPARα antagonist, which suggests that the above effects were mediated through PPARα.

The activation of the PPARγ isoform in the VTA has shown similar results as that of PPARα signaling (De Guglielmo et al., 2015). PPARγ is highly expressed in GABA neurons (Domi et al., 2016) and are thus found in various brain regions such as the VTA and NAc (De Guglielmo et al., 2015) that contain GABAergic neurons (Russo & Nestler, 2013). De Guglielmo et al. (2015) used ex vivo electrophysiology to demonstrate that bath applica- tion of pioglitazone, a selective PPARγ agonist, inhibited morphine-induced augmentation of VTA DA firing rates. Specifically, it was discovered that this attenuation of VTA DA activity is dependent on GABAergic signaling in the rostromedial tegmental nucleus (RMTg)—a brain region that corresponds to the posterior section of the VTA that regulates VTA DA activity through GABAergic innerva- tion (De Guglielmo et al., 2015). The same study reported that oral administration of pioglitazone attenuated the mo- tivation for opioid self-administration in rats. A similar behavioral effect was found through intra-RMTg infusions of pioglitazone which supports the potential mechanism that PPARγ activation in the RMTg regulates VTA DA transmission through modulation of GABAergic signal- ing. Thus, both cannabinoid and PPAR receptor signaling appear to play important roles in the regulation of VTA DA activity states, the dysregulation of which is a criti- cal underlying factor for a wide variety of neuropsychiatric syndromes.

5 | PPAR AND CANNABINOID MODULATION OF THE NUCLEUS ACCUMBENS

Two significant similarities exist between the NAc and the RMTg. First, both the NAc and the RMTg regulate mesolimbic DA activity through GABAergic projections to the VTA. Second, both structures are also known to express PPARγ (De Guglielmo et al., 2015; Russo et al., 2005). These similarities raise an interesting possibility that in- tra-NAc PPARγ agonism can produce similar effects as PPARγ activation in the RMTg and decrease mesolimbic DA activity through inhibitory GABAergic signaling (De Guglielmo et al., 2015). This possibility is supported by a previous preclinical study by Renard, et al. (2016) that explored the effects of CBD in the rat nucleus accumbens shell (NASh), a target locus for the action of current antip- sychotics (Renard, et al., 2016). This study revealed that intra-NASh CBD administration selectively downregu- lates the expression of phosphorylated GSK-3 beta and phosphorylated Akt Serine 473 isoforms, whereas leaving GSK-3 alpha and Threonine 308 isoforms unaffected. Both Akt and GSK-3 signaling are critically involved in the therapeutic effects of antipsychotic medications through functional interactions with DA D2 receptor substrates (Sutton et al., 2007). Mesocorticolimbic levels of GSK-3 levels are also dysregulated in schizophrenia (Kozlovsky et al., 2001) and Akt is an important genetic biomarker for cannabis-induced psychiatric side-effect vulnerabilities (Di Forti et al., 2012).

Furthermore, chronic intra-NASh CBD treatment resulted in upregulated phosphorylated P70s6K expression, coupled with increased phosphorylation of its downstream effector protein, mammalian Target of Rapamycin (mTOR), which are known to be dysregulated in mood disorders (Jernigan et al., 2011). This study also revealed that chronic CBD treatment strongly mitigates amphetamine (AMPH)-induced sensitization of VTA DA neurons and amphetamine-induced behavioral abnormalities (Renard, et al., 2016). Further behavioral experiments also demonstrated that intra-NASh CBD blocks AMPH-induced sensorimotor gating deficits, hyperlocomotion, and stereotyped behaviors, all of which are well-characterized preclinical animal models of schizophrenia. In a study by Norris et al. (2016), in vivo electrophysiology experiments demonstrated that intra-NASh CBD decreases VTA DA activity through the modulation of GABA signaling (Norris et al., 2016). The intra-NASh administration of CBD with a 5-HT1A antagonist blocked the decrease in VTA DA activity which suggests that CBD produces its effects through 5-HT1A activation in the NASh (Norris et al., 2016). However, CBD can produce effects beyond the 5-HT1A receptor (Russo & Nestler, 2013) which raises the possibility that CBD may decrease VTA DA activity through multiple receptor substrates.

Interestingly, systemic exposure to CBD, PPAR agonists, and omega-3 all appears to have similar effects on NAc DA levels. Galaj et al. (2019) recently reported that systemic CBD blocks cocaine-induced augmentation of DA levels in the NAc (Galaj et al., 2019) which raises the possibility that CBD decreases VTA DA release into the NAc. Similarly, oral administration of the PPARγ agonist pioglitazone has been shown to abate heroin-induced el- evations of extracellular DA in the NASh (De Guglielmo et al., 2015). Furthermore, PPARα activation decreases nicotine-induced elevations of DA in the NAc (Mascia et al., 2011; Panlilio et al., 2012). In line with these find- ings, further evidence suggests that adequate omega-3 consumption is required to properly regulate mesolimbic DA levels as omega-3 deficient diets have been shown to abnormally elevate basal DA levels in the NAc (Zimmer et al., 2000). Altogether, these findings raise the possibil- ity that CBD and omega-3 may regulate mesolimbic DA activity through PPAR signaling, either via independent

pathways or through synergistic mechanisms acting at nuclear PPAR sites.

6 | PPAR AND CANNABINOID MODULATION OF THE PREFRONTAL CORTEX

Considerable evidence implicates dysregulated cortical cannabinoid receptor signaling in various cognitive and affective deficits characterizing neuropsychiatric disorders including schizophrenia and major depressive disorder (Andréasson et al., 1987, 1989; Degenhardt, 2003; Lynskey et al., 2004). Indeed, CB1Rs are abundantly expressed within the medial prefrontal cortex (mPFC) and critically regulate learning and memory mechanisms via control of inhibitory signaling and emotional information processing (Volk & Lewis, 2016). For example, systemic administration of THC or the CB1R agonist WIN 55,212–2 each increase the firing rates and bursting activity of DAergic projections from the VTA to mPFC (French, 1997; Gessa et al., 1998). Furthermore, pharmacological activation of prelimbic mPFC CB1Rs with WIN55-212,2 bi-phasically controls VTA DA neuronal activity states, with low doses causing a strong activation of DAergic firing and bursting rates and higher doses causing decreased activity in VTA DA neurons. Interestingly, these changes in VTA DAergic activity states corresponded to changes in salience attribution and emotional fear-memory formation, as higher activation states potentiated normally non-salient fear memories and inhibition of DAergic activity cause significant blunting of normally salient associative fear memories (Draycott et al., 2014). This dysregulation in emotional salience processing is a critical endophenotype in schizophrenia psychopathology.

In contrast, CBD moderates extracellular levels of cortical DA and opposingly regulates signal transduction cascades linked with chronic THC exposure and schizophrenia including the mTOR/P70S6K pathway within the mPFC (Renard, et al., 2016, 2017). Despite rapidly progressing insights into the antipsychotic properties of CBD, the precise pharmacological mechanisms responsible for its therapeutic efficacy remain elusive.

Although CBD is recognized for its diverse pharmacodynamic profile (Pertwee, 2008), the role of PPAR signaling in CBD's clinical value has received little attention. In line with the proposed PPAR activation profile underlying the antipsychotic actions of CBD, inhibition of PPARα induces aberrant psychotomimetic drug responses, and cognitive inflexibility marked by perseverative behaviors (D'Agostino et al., 2015). The same study found that genetic ablation of PPARγ subtypes engenders morphological abnormalities including reduced expression of parvalbumin (PV)-positive GABAergic interneurons in cortical and hippocampal regions, cortical NMDAR hypofunction, and a schizophrenia-like behav- ioral phenotype that is rescued via systemic administration of the antipsychotic risperidone (D'Agostino et al., 2015). Interestingly, intra-mPFC NMDAR blockade preferentially disinhibits local pyramidal neuronal activity by blunting activity of fast-spiking PV-expressing GABAergic interneurons (Markram et al., 2004; Wilson et al., 1994), and patients with schizophrenia frequently exhibit diminished expression of mPFC PV-expressing interneurons, possibly due to chronic NMDAR desensitization (Cho et al., 2006; Gallinat et al., 2004; Gonzalez-Burgos & Lewis, 2012; Minzenberg et al., 2010). PV-expressing interneurons are posited as necessary for the generation of gamma oscillations (30–80 Hz) throughout the brain, which importantly subserve several cognitive functions, and are also disturbed in schizophrenia (Barr et al., 2010; Benes et al., 2007). Pharmacological activation of intra-mPFC PPARα also improves several cognitive and behavioral functions following ketamine administration in a preclinical model of schizophrenia (D'Agostino et al., 2015), collectively indicating that appropriately maintained PPARα signaling is required for healthy cognition and mPFC-mediated DA function. As such, CBD may promote PPARα signaling in the mPFC to regulate local GABAergic transmission, thereby attenuating impairments in mPFC excitatory-inhibitory balance that are associated with pro-psychotic and cognitive disturbances following adolescent CB1R activation, as well as in patients with schizophrenia (Cass et al., 2014; Renard, et al., 2017). Alternatively, given the current lack of direct evidence for agonist effects of CBD at the PPARγ subtype, CBD might indirectly modulate endocannabinoids or other modulators of PPARγ via inhibition of FAAH. In this case, CBD, through its ability to inhibit FAAH signaling (Bisogno et al., 2001; De Petrocellis et al., 2011) may increase endogenous AEA levels which in turn could directly activate PPARα substrates (O'Sullivan, 2007). Such a functional mechanism for the effects of CBD on PPARα signaling substrates is supported by evidence showing that ethanolamides can suppress the activation of mesolimbic DA neurons through PPARα receptors, particularly in the context of psychoactive drugs of abuse, such as nicotine (Melis et al., 2008).

Disturbances in cortical excitatory-inhibitory balance are consistently observed in schizophrenia and may be responsible for dysregulation of subcortical DA in the disorder (McNamara et al., 2007, 2017). In line with the proposed neuroprotective actions of PPAR activation and CBD on VTA DA signaling and schizophrenia symptomology, deficits in serum-derived DHA are associated with elevated extracellular glutamate in the mPFC (McNamara et al., 2017), and intracranial DHA deficits alter the morphological properties of phospholipid bilayers of particular neuronal and glial subtypes, consequently redistributing presynaptic ves- icles within DA terminals and increasing basal levels of

extracellular DA in cortical and subcortical regions (Tanaka et al., 2012). Furthermore, increased cortical PPAR gamma expression has been observed in patients with schizophrenia (García-Bueno et al., 2016), which may represent a compensatory response to counteract deficiencies in mPFC DHA levels (McNamara et al., 2007). However, increased ratios of intracranial AA:DHA are also observed in schizophrenia (McNamara et al., 2007), and the antipsychotic actions of CBD on positive and negative symptoms are associated with increased 2-AG and AEA serum levels (Leweke et al., 2012), suggesting that increased endocannabinoid signaling may be involved in moderating mPFC-induced subcortical DA dysregulation. Recent preclinical evidence also indicates that increased mPFC high-gamma oscillatory frequencies and neuronal firing rates are linked with the persistent increase in VTA DAergic tone following adolescent THC exposure (Renard, et al., 2017). Disturbances in γ-band oscillatory states are well-established neuronal phenotypes associated with schizophrenia-related psychopathology and are believed to represent an aberrant imbalance between excitatory versus inhibitory neuronal elements across various brain circuits (Williams & Boksa, 2010).

Remarkably, these persistent neural aberrations can be rescued by pharmacological activation of GABAa receptor signaling in the mPFC (Renard, et al., 2017), suggesting that disturbances in mPFC inhibitory control may govern the long-term dysregulation of subcortical DA signaling following adolescent cannabis exposure, as well as increased prevalence of psychopathology during later adulthood (Andréasson et al., 1987; Renard et al., 2016). Interestingly, therapeutic benefits of GABA-modulating drugs have been demonstrated to reduce cognitive and emotional deficits in the methylazoxymethanol acetate (MAM) rodent model of schizophrenia (Gill et al., 2011), and to also improve deficits in working memory and cognitive control, and normalize abnormalities in gamma frequency (Delini-Stula et al., 1992; Renard, et al., 2017). Thus, the antipsychotic actions engendered by CBD may be related to regulatory actions on PV-expressing interneurons or its ability to normalize gamma amplitudes in cortical regions following chronic NMDA receptor activation. Indeed, a recent preclinical study has demonstrated that CBD can strongly reverse the pro-psychotic effects of THC exposure on γ-band oscillatory disturbances in the mesolimbic system via direct actions in the ventral hippocampus (Hudson et al., 2019). These reports warrant an expanded investigation into the activity of other members of this PPAR-N6-N3 pathway and their potential interactions with the antipsychotic and other purported therapeutic properties of CBD. In Figure 2, we present a simplified schematic summary of several of the main reported effects of CBD and Omega-3 mesocorticolimbic signaling and their downstream effects on PPAR-mediated intracellular signaling pathways.

7 | IMPLICATIONS OF OMEGA-3 DIETS IN PPAR AND CANNABINOID SIGNALING

The volume of omega-3 obtained through the diet may have other important implications on PPAR and cannabinoid signaling. As mentioned previously, brain levels of omega-3 are directly correlated with omega-3 levels in the diet (Lafourcade et al., 2011; Yamada et al., 2014). Therefore, a diet rich with omega-3 could theoretically lead to increased PPAR activation in brain regions such as the NAc and RMTg to attenuate VTA DA signaling. A study by Hajjar et al. (2012) reported that a high ratio of omega-3 to omega-6 in the diet increased the expression of PPARα and PPARγ directly in the rat hippocampus (Hajjar et al., 2012). Future research is needed to determine whether omega-3-rich diets can increase PPAR expression in other brain regions such as VTA, NAc, and PFC and how such adaptations may impact neuropsychiatric phenomena. However, if omega-3 supplementation does increase PPAR expression in these brain regions, this would theoretically enhance PPAR signaling by CBD and omega-3 and potentially amplify their efficacy. Interestingly,

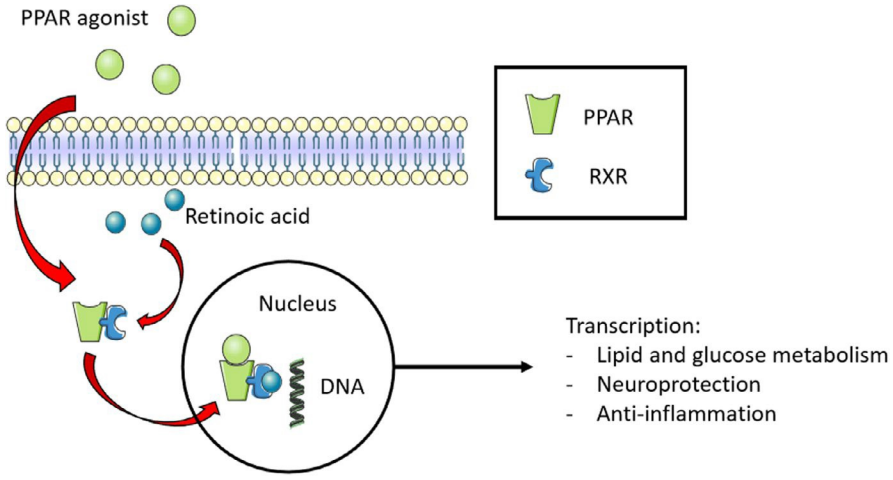

FIGURE 2 Activated intracellular PPAR/RXR complex is transported into the cell nucleus to promote DNA transcription modulating lipid/glucose metabolism, neuroprotective responses, and inflammation. PPAR: Peroxisome Proliferator-Activated Receptors; RXR: Retinoid-X Receptor

an adequate supply of dietary omega-3 has also been implicated in the proper functioning of the endocannabinoid system (Lafourcade et al., 2011; Yamada et al., 2014). Dietary deficiency of omega-3 has been shown to prohibit proper functioning of the CB1 receptor (Lafourcade et al., 2011; Yamada et al., 2014) whereas a diet rich in omega-3 increases the sensitivity of CB1. These findings support the notion that omega-3 is crucial for the modulatory functions of the endocannabinoid system.

8 | CONCLUSIONS

Current evidence supports the potential of CBD and omega-3 as effective regulators of DA activity and promising treatment options for neuropsychiatric disorders such as anxiety disorders, addiction, and schizophrenia. However, the exact mechanisms underlying the effects of CBD and omega-3 remain unclear. Emerging evidence implicates PPARs, which are activated by CBD and omega-3, in the regulation of DA signaling and the neuropsychiatric pathology of anxiety, addiction, and schizophrenia. At the present time, however, there are no studies that have investigated the PPARs as a potential convergence point for the regulation of mesocorticolimbic DA activity and the therapeutic effects of CBD and omega-3 for neurological disorders. Further research is needed to determine whether PPAR activation by CBD and omega-3 is responsible for these effects.

If CBD and omega-3 induce their effects through PPARs, what are the primary brain areas in which PPAR signaling regulates mesocorticolimbic DA activity and decreases neuropsychiatric symptoms? Various brain regions including the PFC, NAc, and the VTA are involved in mesocorticolimbic DA signaling regulation and the pathology of neuropsychiatric disorders. PPARs are expressed in all of these brain regions and further research is required to determine which brain regions are primarily responsible for the mentioned effects of CBD, omega-3, and other PPAR agonists.

A greater understanding of the receptor mechanisms underlying the beneficial effects of CBD and omega-3 may lead to the development of future treatment interventions for various neurological disorders. For example, if CBD and omega-3 are discovered to produce synergistic effects through the common PPAR, medical cannabis formulations with high levels of CBD, omega-3, and/or PPAR agonists may be used to counter the psychotropic effects of THC. CBD, omega-3, and PPAR agonists such as pioglitazone are all substances with a very safe profile. Pioglitazone is an oral drug with a favorable profile that is currently used for type 2 diabetes treatment. Furthermore, there are currently no psychoactive and addictive properties associated with CBD whereas omega-3 are essential fatty acids. The favorable safety profiles further highlight the potential of CBD, omega-3, and PPAR agonists and raises the possibility for fast translation toward future clinical treatments.

One critical question that remains unanswered is how activation of nuclear PPARs modulates downstream genes and proteins linked to the neuropathophysiology of specific neuropsychiatric disorders. PPARs are known to heterodimerize with the retinoid X receptor, following which the complex binds to its specific region on various DNA targets and thereby modulates its target genes (Forman et al., 1996). However, the mechanism by which this dimerization process leads to modulation of target genes within neuronal substrates is largely unknown, particularly within the mesocorticolimbic circuitry. While the primary function of the PPARs is in the regulation of lipid and glucose metabolism, PPAR signaling is also linked to regulation of neuronal differentiation, control of inflammatory responses, and inhibition of various neurodegenerative processes (Quintanilla et al., 2014). For example, activation of PPARγ has been shown to inhibit neuronal damage in the substantia nigra following cerebral ischemia (Zuhayra et al., 2011). In addition, activation of PPARγ has been shown to strongly inhibit inflammatory cytokine release and αβ deposition levels in rodent models of Alzheimer's pathology (Mandrekar et al., 2012). Interestingly, Omega-3 fatty acids and CBD are known to produce similar anti-inflammatory effects (Layé et al., 2018; Nagarkatti et al., 2009) in various neuropathological states, further underscoring the potential synergistic and therapeutic effects these diverse compounds may produce via common mechanisms on the PPAR nuclear system. Importantly, multiple neuropsychiatric conditions are now understood to involve critical neuroinflammatory processes in their underlying pathophysiology. Nevertheless, there is a critical need to elucidate the specific gene substrates and associated protein biomarkers associated with the putative pharmacotherapeutic potential of these substances, particularly as they relate to modulation of selective neurochemical substrates and neuronal populations associated with neuropsychiatric pathology. Advances in single-cell proteomic and genomic mapping will be of substantial benefit in addressing these urgent research questions.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTION

T.J. wrote the manuscript and conducted literature reviews. R.H. co-wrote the manuscript and created the figures. W.R. reviewed and edited the manuscript and provided intellectual input. S.R.L. reviewed and edited the manuscript and

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