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Review

REVIEW

High Times for Painful Blues: The Endocannabinoid System in Pain-Depression Comorbidity

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Abstract

Depression and pain are two of the most debilitating disorders worldwide and have an estimated cooccurrence of up to 80%. Comorbidity of these disorders is more difficult to treat, associated with significant disability and impaired health-related quality of life than either condition alone, resulting in enormous social and economic cost. Several neural substrates have been identified as potential mediators in the association between depression and pain, including neuroanatomical reorganization, monoamine and neurotrophin depletion, dysregulation of the hypothalamo-pituitary-adrenal axis, and neuroinflammation. However, the past decade has seen mounting evidence supporting a role for the endogenous cannabinoid (endocannabinoid) system in affective and nociceptive processing, and thus, alterations in this system may play a key role in reciprocal interactions between depression and pain. This review will provide an overview of the preclinical evidence supporting an interaction between depression and pain and the evidence supporting a role for the endocannabinoid system in this interaction.

Keywords: depression, pain, anandamide, cannabinoid, stress

Clinical Data Supporting Depression-Pain Comorbidity

Depression and pain are two of the most prevalent psychiatric and neurological disorders worldwide, and both are associated with significant disability, impaired health-related quality of life, and high mortality (Spitzer et al., 1995; Kvien, 2004; Scholich et al., 2012; Hassett et al., 2014). While each is considered a debilitating disorder in its own right, these disease entities frequently coexist, and it has been reported that this association may be as high as 80% of patients (Poole et al., 2009). For example, major depressive and bipolar disorder is associated with painful symptoms in up to 95% of patients (Grover et al., 2012; Maneeton et al., 2013; Nicholl et al., 2014). Similarly, patients suffering from inflammatory and neuropathic pain are up to 4.9 times more likely to develop depression or anxiety disorder than the general population (Hawker et al., 2011; Knaster et al., 2012; Emery et al., 2014; Lin et al., 2015). Patients exhibiting comorbid depression and pain do not respond as effectively to pharmacological treatment, and this comorbidity is more disabling and expensive to both patients and society than either condition alone (Emptage et al., 2005; Gameroff and Olfson, 2006). Furthermore, it has also been found that the severity of depression directly correlates with increased severity of pain symptomatology (Khongsaengdao et al., 2000). However, it should be noted that an intricate relationship exists between depression and pain such that although pain is commonly reported by depressed patients, examination of pain thresholds to various stimuli such as cold, heat, and pressure have been shown to be reduced, increased, or unchanged (Ben-Tovim and Schwartz, 1981; Lautenbacher et al., 1999; Gormsen et al., 2004; Bar et al., 2005; Boettger et al.,

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2013), effects which depend on the modality and intensity of the stimulus. Thus, given the complex interaction between affect and pain, and the high comorbidity of depression-pain, greater understanding of the neurobiological mechanisms underlying the association is warranted to develop more efficacious treatment strategies. There have been several studies investigating the role of neural substrates, including neuroanatomical organization, neurotransmission, neurotrophins, dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis, and inflammation, to name but a few, in the interaction between affect and nociceptive processing (for review, see Blackburn-Munro, 2004; Goesling et al., 2013; Walker et al., 2014). A full review of the role of each of these substrates is beyond the scope of this review. However, increased evidence has indicated a role for a further substrate, the endogenous cannabinoid (endocannabinoid) system, in affective and nociceptive responding (for reviews, see Finn, 2010; Ashton and Moore, 2011; Gorzalka and Hill, 2011; Rani Sagar et al., 2012; Hillard and Liu, 2014; Jennings et al., 2014; Boychuk et al., 2015) and as such, alterations in this system may provide a common mechanism by which depression and pain coexist. Preclinical animal models provide a valuable means of investigating potential neurobiological substrates that may underlie the association between depression and pain. As such, this review will provide an overview of the preclinical evidence supporting an interaction between depression and pain, the evidence supporting a role for the endocannabinoid system in this interaction, and the potential mechanisms through which the endocannabinoid system may mediate effects on affect and nociceptive processing.

Preclinical Animal Models Support Depression-Pain Interactions

Animal Models of Depression Exhibit Altered Nociceptive Responding

Several animal models of depression based on genetics, stress, lesion, and pharmacological manipulation have been shown to exhibit alterations in nociceptive responding (for review, see Li, 2015), supporting the clinical finding of an association between depression and pain. For example, in rats, the chronic mild stress model of depression has been shown to display a reduced nociceptive threshold to cold (Bardin et al., 2009; Bravo et al., 2012; Bravo et al., 2014) and mechanical (Bardin et al., 2009; Imbe et al., 2012) stimuli and an increased threshold to noxious thermal stimuli (Shi et al., 2010). Furthermore, both inflammatory (Gameiro et al., 2005; Rivat et al., 2010; Wang et al., 2013) and neuropathic (Bravo et al., 2012) pain behavior are enhanced in chronic stress models of depression. Similarly, we and others have shown that the Wistar-Kyoto (WKY) rat, a stress hyperresponsive rat strain with a depressive-like phenotype, exhibits thermal hyperalgesia (Burke et al., 2010), visceral hyperalgesia to colorectal distension (Gibney et al., 2010; Gosselin et al., 2010; O'Malley et al., 2010), enhanced formalin-evoked inflammatory pain behavior (Burke et al., 2010; Rea et al., 2014), and enhanced mechanical allodynia following peripheral nerve injury (neuropathic pain) (Zeng et al., 2008; del Rey et al., 2011). Reserpine-induced monoamine depletion has long been known to result in depressive-like behavior, and recent evidence has demonstrated accompanying thermal allodynia (Liu et al., 2014), as well as pronounced and long-lasting mechanical hyperalgesia and allodynia, and cold allodynia (Nagakura et al., 2009; Arora et al., 2011). Thus, this model has been proposed as a possible rodent model of fibromyalgia (Nagakura et al., 2009). Furthermore, recent work from our group has demonstrated that the olfactory bulbectomised rat, a lesion model of depression, exhibits increased sensitivity to mechanical and thermal stimuli in the von Frey, acetone drop, hot plate, and tail flick tests (Burke et al., 2010, 2013), increased inflammatory pain responding in the formalin test (Burke et al., 2010), and enhanced neuropathic pain responding following spinal nerve ligation (Burke et al., 2013, 2014). Thus, taken together, several animal models of depression have been shown to exhibit altered nociceptive thresholds and enhanced inflammatory and neuropathic pain behavior, mimicking effects observed clinically.

Animal Models of Chronic Pain Exhibit Depressive-Like Behavior

Depressive- and anxiety-like behavior, as assessed by multiple paradigms, has been reported in a wide variety of preclinical models of chronic pain (for review, see Yalcin et al., 2014; Li, 2015). For example, peripheral or spared nerve injury in mice induces a pronounced mechanical allodynia accompanied by the development of depressive-like behavior as determined by enhanced immobility in the forced swim test (FST) (Goncalves et al., 2008; Norman et al., 2010; Wang et al., 2011). Similarly, rodents subjected to the chronic constriction injury model of neuropathic pain exhibit reduced sucrose preference (Dellarole et al., 2014) and increased immobility in the FST (Hu et al., 2009; Jesse et al., 2010; Fukuhara et al., 2012; Zhao et al., 2014), indicating the development of anhedonia and behavioral despair, hallmarks of depressive-like behavior. In the complete Freund's adjuvant model of inflammatory pain, both mice and rats exhibited depression-like behavior in the FST (Maciel et al., 2013; Borges et al., 2014) and tail suspension test (Maciel et al., 2013) and anxiety-related behavior in the elevated plus maze, open field test, and social interaction test (Parent et al., 2012; Borges et al., 2014). Such changes in affective processing in chronic pain models have been shown to occur later than the development of enhanced somatosensory perception. For example, in neuropathic pain models, alterations in emotional behavior have been observed 4 to 8 weeks post nerve injury (Suzuki et al., 2007; Yalcin et al., 2011), but not prior to this (2-4weeks) when mechanical allodynia/hypersensitivity is observed (Kontinen et al., 1999; Hasnie et al., 2007). These studies highlight the development of depressive- and anxiety-like behavior in models of neuropathic or inflammatory pain and suggest that pathological alterations induced by persistent nociceptive input to brain regions that process both pain and affect may account, at least in part, for comorbid depressive-like behavioral changes.

Animal models that replicate the clinical scenario are important for in-depth investigation of the possible neurobiological substrates that may mediate the association between depression and chronic pain. Although the cause of this coexistence remains somewhat elusive, as highlighted earlier, common anatomical substrates and neurobiological mediators, including neurotransmitters, neurotrophins, neuroendocrine alterations, and inflammatory mediators, have been identified, any or all of which may alter neural functioning in key brain regions involved in regulating emotional and nociceptive processing (for review, see Blackburn-Munro, 2004; Maletic and Raison, 2009; Anderson et al., 2012; Goesling et al., 2013; Meerwijk et al., 2013; Jennings et al., 2014; Walker et al., 2014; Doan et al., 2015). Increasing evidence has highlighted an important role for the endocannabinoid system in modulating emotional and

nociceptive processing, and thus this system may play a key role in the association between pain and depression.

The Endocannabinoid System

The plant *Cannabis sativa* has been used as a medicine throughout the world for several thousand years, with reports of its use in treating painful symptoms appearing as early as 2600 BC. The principal psychoactive ingredient of *Cannabis sativa*, delta-9-tetrahydrocannabinol (Δ^9-THC), was first identified in 1964 (Gaoni and Mechoulam, 1964), and subsequent studies to understand its mechanism of action led to the discovery of the endogenous cannabinoid (endocannabinoid) system. This endocannabinoid system consists of the cannabinoid receptors (CB_1 and CB_2) (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993), their naturally occurring endogenous ligands (the best characterized of which are N-arachidonoylethanolamine, or anandamide [AEA]) (Devane et al., 1992) and 2-arachidonylglycerol (2-AG) (Mechoulam et al., 1995), and the enzymes involved in their biosynthesis and degradation. Other endocannabinoid ligands have also been identified, including oleamide (Leggett et al., 2004), O-arachidonoyl ethanolamine (virodhamine) (Porter et al., 2002), 2-arachidonoyl glycerol ether (noladin ether) (Hanus et al., 2001), and N-arachidonoyl-dopamine (Huang et al., 2002), although their physiological role has not been examined in detail. Endocannabinoid biosynthesis occurs on demand via hydrolysis of cell membrane phospholipid precursors. AEA is formed from the precursor *N*-arachidonoylphosphatidylethanolamine due to the hydrolytic activity of the phospholipase D enzyme NAPE-PLD (Di Marzo et al., 1994; Sugiura et al., 1996), while fatty acid amide hydrolase (FAAH) is the primary enzyme responsible for the metabolism of this endocannabinoid (Cravatt et al., 1996). In comparison, the main biosynthetic pathway for 2-AG involves the hydrolysis of the membrane phospholipid phosphatidylinositol by phospholipase C, producing 1,2-diacylglycerol, which is then converted to 2-AG by diacylglycerol lipase (Prescott and Majerus, 1983, Sugiura et al., 1995). 2-AG is primarily metabolized by monoacylglycerol lipase (MAGL) (85%) (Blankman et al., 2007), although other enzymes including cyclooxygenase-2 (Yu et al., 1997; Kozak et al., 2000), lipoxygenase (van der Stelt et al., 2002), ABDH6 (serine hydrolase α/β-hydrolase domain), and ABDH12 (Blankman et al., 2007), have also been shown to play a role.

Upon release, endocannabinoids bind and activate the G-protein coupled receptors CB_1 and/or CB_2. CB_1 receptors are highly expressed on presynaptic neurons throughout the human and rodent brain (Herkenham, 1991; Tsou et al., 1998; Mackie, 2008), the activation of which results in inhibition of cyclic AMP, activation of mitogen-activated protein kinase, inhibition of N- and P/Q-type voltage-activated Ca^{2+} channels, and induction of inwardly rectifying K+ currents, with the resultant inhibition of neurotransmitter release (Demuth and Molleman, 2006). CB_1 receptors have also been shown to be expressed on glia and a wide range of peripheral tissues, though at lower levels than observed on neurons (Galiegue et al., 1995; Carlisle et al., 2002; Osei-Hyiaman et al., 2005; Cavuoto et al., 2007; Cota, 2007). In contrast, CB_2 receptors are widely distributed in peripheral tissues and organs, with a particularly high density on immune cells and tissues (Munro et al., 1993; Berdyshev, 2000; Sugiura et al., 2000), including on glia within the brain, with enhanced expression observed under neuroinflammatory conditions (Carlisle et al., 2002; Nunez et al., 2004; Rock et al., 2007). Accumulating evidence has also indicated that the CB_2 receptor is also expressed on subsets of neurons within the brain (Van Sickle et al., 2005; Gong et al., 2006; Baek et al., 2008; Zhang et al., 2014) and thus also modulates neurotransmission (Roche and Finn, 2010; Atwood et al., 2012; Kim and Li, 2015). Endocannabinoids also have affinity for and activity at other receptors, namely the transient receptor potential vanilloid 1, peroxisome proliferator-activated receptors, GPR55, and GPR119 (Huang et al., 2002; Overton et al., 2006; Sun et al., 2006; Ryberg et al., 2007). Activity at these receptors has been proposed to account, at least partially, for some of the differential effects observed with potent selective cannabinoid agonists and pharmacological modulators of endocannabinoid tone.

Because of the distribution of the endocannabinoid system throughout spinal and supraspinal regions, it is in a prime position to regulate neurophysiological activities such as affective and nociceptive processing. This has been a very active area of research over the past decade, with a number of excellent reviews synthesizing the data supporting a role for the endocannabinoid system in modulating mood and nociception (for review, see Ashton and Moore, 2011; Gorzalka and Hill, 2011; Rani Sagar et al., 2012; Hillard and Liu, 2014; Ulugol, 2014; Boychuk et al., 2015). However, no review to date has examined the evidence that may support a role for the endocannabinoid system as a link between depression and pain, and thus the remainder of this review aims to collate and synthesize these data.

The Role of the Endocannabinoid System In Depression-Pain Interactions

Clinical Evidence

Several lines of evidence have demonstrated alterations in the endocannabinoid system in chronic pain (Richardson et al., 2008; Kaufmann et al., 2009) and in psychiatric patients (Gobbi et al., 2005; Hill and Gorzalka, 2005; Koethe et al., 2007). For example, various polymorphisms of CB_1 and CB_2 receptors have been identified in patients with major depression and bipolar disorder (Monteleone et al., 2010; Minocci et al., 2011; Mitjans et al., 2012; Mitjans et al., 2013) with a single nucleotide polymorphism in the CB_1 receptor reported to enhance the risk of treatment resistance in depression (Domschke et al., 2008) and the development of anhedonic depression following early life trauma (Agrawal et al., 2012). Similarly, genetic alterations in the CB_1 receptor and FAAH have also been identified in patients with pain associated with migraine, Parkinson's disease, and irritable bowel syndrome (Juhasz et al., 2009; Park et al., 2011; Greenbaum et al., 2012). In addition, serum levels of endocannabinoids have been reported to be reduced in both depressed patients (Hill et al., 2008c, 2009b) and chronic pain patients (Fichna et al., 2013). A recent study has reported enhanced plasma 2-AG levels and increased CB_1 and CB_2 mRNA expression on blood lymphocytes in osteoarthritic patients (La Porta et al., 2015). A significant positive correlation was observed between 2-AG levels, pain, and depression, and a negative correlation of 2-AG with quality of life and visual memory was observed (La Porta et al., 2015). In addition, CB_1 receptor expression was positively correlated with depression scores, while CB_2 receptor expression was correlated with pain scores. These data indicate that key components of the endocannabinoid system are upregulated in human osteoarthritis with significant correlations with pain and emotional symptoms. In addition to visual loss and sensory deficits, neuromyelitis optica is associated with significant pain (altered threshold responding and symptoms of neuropathic pain), depression, and increased plasma levels of 2-AG and

AEA (Pellkofer et al., 2013). This study evaluated if a correlation existed between pain threshold and levels of endocannabinoids, demonstrating a considerable negative correlation between the plasma levels of 2-AG and mechanical pain thresholds in these patients, although this study did not evaluate if an association also existed with depressed mood. While the data suggest a possible association between pain, depression, and the endocannabinoid system in osteoarthritis and neuromyelitis optica patients, further clinical studies are required to determine if alterations in the genetics, levels, and activity of the endocannabinoid system exist in other patient groups exhibiting depression-pain comorbidity.

There has been a paucity of clinical studies directly investigating the role or activity of cannabinoids in depression-pain interactions; however, enhanced mood and improved quality of life have been reported in studies investigating the analgesic efficacy of cannabinoid-based therapies (Table 1). For instance, cannabis intake has been reported to improve muscle and nerve pain as well as depression and anxiety symptomatology in a group of HIV patients (Woolridge et al., 2005). Improvements in anxiety and overall distress have been reported in patients with advanced cancer in whom pain symptoms were managed by daily adjunctive administration of Cesamet (nabilone, a Δ⁹-THC analogue) for 30 days (Maida et al., 2008). Similarly, a randomized, double blind, placebo-controlled trial, which examined the therapeutic benefit of nabilone in terms of pain management and quality of life improvement in patients with fibromyalgia, identified significant pain relief and alleviation of anxiety symptoms after 4 weeks of therapy (Skrabek et al., 2008). In addition, a retrospective evaluation investigating the efficacy of nabilone for the management of concurrent disorders in seriously mentally ill correctional populations identified significant amelioration of symptoms related to posttraumatic stress disorder as well as a subjective improvement in chronic pain (Cameron et al., 2014). Furthermore, a multicenter retrospective survey of patients with chronic central neuropathic pain or fibromyalgia who were prescribed oral Δ⁹-THC (dronabinol), supplemental to existing medication, reported improved symptoms of both anxiety and depression after 7 months of treatment as assessed by the Hospital Anxiety and Depression Scale (Weber et al., 2009). Although Sativex (1:1 ratio of Δ⁹-THC:cannabidiol), indicated for resistant spasticity and pain in multiple sclerosis, has not yet been directly associated with significant mood changes, patients have reported improvements in overall quality of life following 16 weeks of treatment (Vermersch, 2011). In a separate randomized control clinical trial evaluating the effect of Sativex in patients with chronic painful diabetic neuropathy, patients with comorbid depression displayed significant improvements in total pain score in comparison with nondepressed counterparts (Selvarajah et al., 2010). Collectively, the above studies suggest that when coexistent, both depression/anxiety and pain respond to exogenously administered cannabinoids, although it remains to be determined if the effects are mediated by common or parallel mechanisms. Recent evidence has demonstrated enhanced amygdala activity and reduced functional connectivity between the amygdala and somatosensory cortex correlate with Δ⁹-THC–mediated reductions in the unpleasantness to ongoing pain (Lee et al., 2013), suggesting that the amygdala may provide a common neural circuit for the association between emotional responding and pain.

Preclinical Evidence

Despite numerous reports of altered endocannabinoid signaling in various animal models of pain (Lim et al., 2003; Zhang et al., 2003; Walczak et al., 2005; Mitrirattanakul et al., 2006) and mood-related behavior (Vinod et al., 2012; Marco et al., 2014; Navarria et al., 2014), there is limited direct evidence available identifying alterations in endocannabinoid function in animal models of coexistent depressive and pain behavior (Tables 2 and

Table 1. Clinical Studies Demonstrating Effects of Cannabinoid-Based Therapies on Symptoms of Comorbid Depression and Pain

	Drug	Pain Measurement	Depression/ Anxiety Measurement	Outcomes in Pain	Outcomes in Depression/ Anxiety	Reference
HIV	Cannabis	Pilot questionnaire	Pilot Questionnaire	↓ muscle, ↓ nerve pain, headaches	↓ anxiety, depression	Woolridge et al. (2005)
Cancer pain	Nabilone (Cesamet®)	ESAS MSE	ESAS	↓ pain score, MSE	↓ anxiety, overall stress	Maida et al. (2008)
Fibromyalgia	Nabilone	VAS FIQ	Anxiety	↓ pain	↓ anxiety	Skrabek et al. (2008)
Mentally ill offenders	Nabilone	Self-reported pain severity	PCL-C GAF	↓ pain	↓ PTSD symptoms	Cameron et al. (2014)
Multiple sclerosis-related resistant spasticity	Sativex (Δ⁹-THC, cannabidiol)	NRS spasticity score	QOL	↓ spasticity	↑ QOL	Vermersch (2011)
Chronic central neuropathic pain, fibromyalgia	Δ⁹-THC	VRS, NRS, PDI	SF-12, QLIP, HADS,	↓ pain, pain intensity	↑ QOL, depression, ↓ anxiety	Weber et al. (2009)
Painful diabetic peripheral neuropathy	Sativex (Δ⁹-THC, cannabidiol)	VAS	HADS, QOL	↓ pain (only in patients with baseline depression)	↑ QOL	Selvarajah et al. (2010)

Abbreviations: ESAS, Edmonton symptom assessment system; FIQ, fibromyalgia impact questionnaire; GAF, Global Assessment of Functioning; HADS, hospital anxiety and depression scale; HIV, human immunodeficiency virus; MSE, morphine sulphate equivalent; NRS, numerical rating scale; PDI, pain disability index; PCL-C, Posttraumatic Checklist–Civilian version; PTSD, posttraumatic stress disorder; QLIP, quality of life; QOL, quality of life; SF-12, short form-12;VAS, visual analog scale; VRS, verbal rating scale.

3). One of the first studies examining the role of the endocannabinoid system in the interaction between affect and pain was conducted by Takahashi and colleagues (2003). In this study, outbred Swiss-albino mice were stratified into groups of anxious and nonanxious animals as determined by behavioral responses in the elevated plus maze, before subsequent exposure to intraplantar formalin administration (Takahashi et al., 2003). Despite the hypothesis that the degree of anxiety may contribute to the perception of and response to the noxious stimulus, both anxious and nonanxious animals displayed comparable formalin-evoked biphasic nociceptive profiles. Systemic pretreatment with Δ^9-THC elicited an analgesic effect in both groups of animals, an effect blocked by systemic pretreatment with a CB_1 receptor antagonist, rimonabant (Takahashi et al., 2003). These data suggested that the endocannabinoid system (and in particular the CB_1 receptor) may represent a potential treatment strategy for inflammatory pain in the presence and/or absence of anxiety and possibly other neuropsychiatric disorders. However, it should be noted that direct activation of central CB_1 receptors is responsible for the psychoactive effects of potent synthetic or plant-derived cannabinoids; thus potent, direct agonism of this receptor is unlikely to be therapeutically viable for pain and/or psychiatric disorders. In comparison, modulation of endocannabinoid tone by inhibiting enzymes responsible for their metabolism has been proposed to confer improved efficacy and safety relative to direct cannabinoid agonists.

The WKY rat is a genetically stress-sensitive strain of rat that exhibits a depression- and anxiety-related phenotype (Pare and Redei, 1993) and heightened nociceptive behavioral responding in several paradigms (Zeng et al., 2008; Burke et al., 2010). Characterization of the endocannabinoid system in WKY rats has revealed higher levels of FAAH and CB_1 receptor coupling and lower levels of AEA in the frontal cortex and hippocampus when compared with Wistar rats (Vinod et al., 2012). Furthermore, enhancing AEA tone by pharmacologically inhibiting FAAH activity resulted in an attenuation of depressive-like behavior (sucrose preference test and FST) in WKY rats (Vinod et al., 2012). Recent studies in our laboratory have identified alterations in the endocannabinoid system concurrent with enhanced formalin-evoked nociceptive behavior in the WKY rat (Rea et al., 2014) (Table 2). More specifically, we found that in WKY rats, intraplantar administration of the noxious inflammatory pain stimulus formalin resulted in a significant reduction in AEA in the rostral ventromedial medulla (RVM), a component of the descending pain pathway synonymous with pain facilitation and/or inhibition, an effect that was not observed in Sprague Dawley (SD) counterparts. Intraplantar administration of formalin increased levels of 2-AG in the RVM of SD rats, an effect not observed in WKY animals. Furthermore, exposure to formalin induced significant increases in mRNA expression of NAPE-PLD and diacylglycerol lipase-α, precursors of AEA and 2-AG, respectively, in the RVM of SD rats, an effect not observed in the WKY strain. Pharmacological

Table 2. Endocannabinoid-Mediated Effects/Changes on Affective and Nociceptive Behavior in Animal Models

Depression/ Affective Model	Nociceptive Effects	Cannabinoid-based drugs		Endocannabinoid-related changes/effects	Reference
Anxiety-stratified (EPM), mouse	↑ formalin-evoked nociceptive responding in anxious and non-anxious	Δ^9-THC Rimonabant	$CB_{1/2}$ agonist CB_1 antagonist	Δ^9-THC ↓ nociception in both anxious and non-anxious mice, Rimonabant blocked effects of Δ^9-THC	Takahashdi et al. (2003)
WKY rat	↑ formalin-evoked nociceptive responding			Formalin-induced ↓ AEA in RVM, No formalin-induced ↑ 2-AG, NAPE-PLD or DAGL-α in RVM (compared with SD)	Rea et al. (2014)
		URB597 AM251	FAAH inhibitor CB_1 antagonist	Systemic URB597 ↓ nociception Systemic AM251 ↑ nociception AM251 within RVM blocked effect of URB597	
Repeated FST in SD and WKY rat	Stress ↓ formalin-evoked nociceptive responding in SD Stress ↓ formalin-evoked nociceptive responding in WKY			↑ MAGL mRNA in spinal cord of SD ↓ AEA in amygdala of SD No change in MAGL mRNA in spinal cord of WKY No change AEA in amygdala of WKY	Jennings et al. (2015)
CUS, mouse	↓ latency to respond in HPT	URB597 JZL184	FAAH inhibitor, MAGL inhibitor	URB597 ↓ anxiety (EPM, LD) JZL184 ↓ anxiety (LD) Both ↓ thermal hyperalgesia	Lomazzo et al. (2015)
CUS, mouse	Chronic mechanical hyperalgesia following NGF	URB597 JZL184	FAAH inhibitor, MAGL inhibitor	URB597 ↓ hyperalgesia No change with JZL184	Lomazzo et al. (2015)

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; CUS, chronic unpredicted stress; EPM, elevated plus maze; FAAH, fatty acid amino hydrolase; DAGL-α, diacylglycerol lipase-alpha; HPT, hot plate test; LD, light-dark box; MAGL, monoacylglycerol lipase; NAPE-PLD, N-acyl phosphatidylethanolamine-specific phospholipase D; NGF, nerve growth factor; RVM, rostral ventromedial medulla; SD, Sprague Dawley; WKY, Wistar-Kyoto.

Table 3. Endocannabinoid-Mediated Effects/Changes on Affective and Nociceptive Behavior in Animal Models of Pain

Pain Model	Depressive Effects	Cannabinoid-Based Drugs		Endocannabinoid-Related Changes/Effects	Reference
PNL, mouse	↑ Anxiety in LD and Zero Maze ↓ Sucrose Preference in $CB_1^{-/-}$ mice only			Anxiety and depressive effects only in $CB_1^{-/-}$ mice	Racz et al. (2015)
Monosodium iodoacetate, mouse	↑ Anxiety in EPM Memory impairment in object recognition memory task	ACEA JWH133	CB_1 agonist CB_2 agonist	↑ anxiety in $CB_1^{-/-}$ mice no anxiety in $CB_2^{-/-}$ mice ACEA and JWH133 ↓ mechanical allodynia and anxiety ACEA ↓ memory impairment	La Porta et al. (2015)
CCI, rat	↑ Immobility in FST	GW405833	CB_2 agonist	GW405833 ↓ mechanical hyperalgesia GW405833 ↓ immobility	Hu et al. (2009)
Acid-stimulated stretching, rat	↓ Food intake ↓ ICSS	Δ^9-THC, CP55940	$CB_{1/2}$ agonist $CB_{1/2}$ agonist	Both blocked stretching Both exacerbated ↓ ICSS No effect on feeding	Kwilacz et al. (2012)
Acid-stimulated stretching, rat	↓ ICSS	URB597 Rimonabant SR144528	FAAH inhibitor CB_1 antagonist CB_2 antagonist	URB597 ↓ stretching; blocked by rimonabant, URB597 induced delayed partial attenuation of ICSS - not attenuated by rimonabant or SR144528	Kwilacz et al. (2014)

Abbreviations: CCI, chronic constrictive injury; CFA, complete Freud's adjuvant; EPM, elevated plus maze; FAAH, fatty acid amino hydrolase; FST, forced swim test; ICSS, intracranial self-stimulation; LD, light-dark box; MBT, marble burying test; PNL, partial sciatic nerve ligation.

studies were carried out to evaluate the functional significance of the alterations in the endocannabinoid system in WKY rats in response to formalin. Enhancing endogenous AEA tone following systemic administration of the FAAH inhibitor URB597 attenuated formalin-evoked hyperalgesic responding in WKY rats, while in comparison, CB_1 receptor antagonism was associated with augmentation of nociceptive responding. Furthermore, CB_1 receptor blockade within the RVM attenuated the reduction in nociceptive behavior induced by URB597 in WKY rats. In comparison, pharmacological manipulation of the endocannabinoid system in SD rats did not alter formalin-evoked nociceptive responding (Rea et al., 2014). These findings indicate a causative role of endocannabinoid dysregulation in hyperalgesic behavior associated with negative affect, and moreover identify a role for AEA-induced activation of CB_1 receptors in the RVM as a mediator of pain suppression in animal subjects predisposed to anxiety and depression. In addition to its role in influencing responsivity of WKY rats to noxious stimuli in the absence of stress, we have also shown very recently that the endocannabinoid system may also play a role in the differential effects of repeated homotypic stress on inflammatory pain-related behavior in WKY vs SD rats (Jennings et al., 2015). Specifically, repeated forced swim stress exposure prolonged and attenuated formalin-evoked nociceptive behavior in SD and WKY rats, respectively. These behavioral alterations were accompanied by differential effects of stress on AEA levels in the amygdala and MAGL expression in the spinal cord between SD and WKY rats (Jennings et al., 2015). These data indicate that changes in the tone of the endocannabinoid system in the amygdala and spinal cord may underlie the differential effects of stress on inflammatory pain behavior between SD and WKY rats.

The chronic unpredictable stress (CUS) model of depression has been shown to exhibit thermal hyperalgesia in the hotplate test (Lomazzo et al., 2015), cold allodynia (Bravo et al., 2012), exacerbated trigeminovascular nociception (Zhang et al., 2013), inflammatory hyperalgesia in response to formalin administration (Shi et al., 2010), and persistent mechanical hyperalgesia following nerve growth factor administration (Lomazzo et al., 2015). Exposure to CUS has been shown to result in site-specific alterations in the endocannabinoid system, notably a downregulation of CB_1 receptors, reduction in 2-AG levels and increased FAAH levels in the hippocampus (Hill et al., 2005; Reich et al., 2009), an increase in CB_1 receptor mRNA expression in prefrontal cortex and decrease in expression in the midbrain (Bortolato et al., 2007), a decrease in CB_1 receptor density in the hypothalamus and striatum and increased CB_1 receptor density in the prefrontal cortex (Hill et al., 2008a; McLaughlin et al., 2013), a reduction in 2-AG–mediated retrograde synaptic transmission in the hippocampus (Zhong et al., 2014), and a reduction in AEA levels in the hypothalamus, prefrontal cortex, hippocampus, and striatum (Hill et al., 2008a). Depressive-like behaviors in the CUS model have been shown to be attenuated by endocannabinoid-modulating pharmacological agents, including the MAGL inhibitor JZL184 (Zhong et al., 2014; Zhang et al., 2015). Only one study to date has examined the effect of endocannabinoid modulation on affective and pain responding in CUS-exposed mice. Pretreatment with the FAAH inhibitor, URB597, or MAGL inhibitor, JZL184, which enhanced endogenous levels of AEA and 2-AG, respectively, significantly attenuated CUS-induced anxiety-related behavior in the light-dark box and concurrent thermal hyperalgesia (Lomazzo et al., 2015). Long-lasting widespread mechanical hyperalgesia,

induced by intramuscular administration of nerve growth factor to CUS rats, was effectively reduced by URB597, but not JZL184 (Lomazzo et al., 2015). These data demonstrate an important role for AEA signaling in anxiety- and pain-related behavior in stress-exposed mice.

In addition to the evidence supporting a role for the endocannabinoid system in enhanced nociception observed in models of depression, alterations in endocannabinoid signaling have also been observed in animal models of chronic pain with comorbid alteration in affective responding (Table 3). A recent report by Racz and colleagues (2015) has revealed a prominent role of CB_1-mediated events in affective behavior induced by neuropathic pain. In this study, partial sciatic nerve ligation (PNL) was employed to induce a model of neuropathic pain in wild-type and $CB_1^{-/-}$ mice. Wild-type and $CB_1^{-/-}$ mice exhibited mechanical allodynia following PNL. However, evaluation of anxiety- (light-dark test and the elevated zero-maze) and depressive-like (sucrose preference test) behavior 4 to 7 weeks following PNL revealed deficits in affective responding in $CB_1^{-/-}$, but not wild-type, mice (Racz et al., 2015). Thus, these data demonstrate that functionally active CB_1 receptors confer resilience to pain-related anxiety/depression, highlighting a protective role for CB_1 receptors against the emotional consequences of neuropathic pain. In a similar fashion, La Porta et al. (2015) recently investigated the role of the endocannabinoid system in affective and cognitive manifestations in an animal model of osteoarthritis. This study revealed that the anxiety-related behavior of osteoarthritic mice, identified in the elevated plus maze, was enhanced in $CB_1^{-/-}$ and absent in $CB_2^{-/-}$ mice, indicating differential effects of CB_1 and CB_2 receptors in mediating the affective dimension of pain in the model. Similar to effects in a neuropathic model (Racz et al., 2015), the data would indicate that CB_1 receptors confer resilience, while CB_2 receptors confer susceptibility to the development of arthritis-related anxiety. The authors suggest and provide some support that the differential effects of CB_1 and CB_2 receptors may be mediated by alterations in HPA axis functionality and responses (La Porta et al., 2015). In addition, this study also demonstrated that acute pharmacological blockade of CB_1 or CB_2 receptors ameliorated both the nociceptive and affective dimension of pain in the model (La Porta et al., 2015). Taken together, the data suggest that cortico-limbic endocannabinoid signaling is a key modulator of different osteoarthritis pain manifestations.

Only one study to date has investigated the role of CB_2 receptors in the interaction between neuropathic pain and affective behavior. The chronic constriction injury model of neuropathic pain results in mechanical hypersensitivity and depressive-like behavior (immobility in the FST) in mice (Hu et al., 2009). Both depressive-like behavior and mechanical hyperalgesia following constriction injury were significantly attenuated by systemic administration of the CB_2 receptor agonist GW405833, effects that were not observed in sham-operated animals. Furthermore, such behavioral effects were superior to administration of a tricyclic antidepressant, first line treatment for depression and chronic pain (Hu et al., 2009). The precise mechanism by which CB_2 receptor agonism may elicit analgesic and antidepressant-like effects was not evaluated; however, given the well-recognized role for inflammatory processes in mediating chronic pain, it is possible that CB_2 receptor activation attenuates such responses, preventing the development of central sensitization and mechanical allodynia and the associated increase in neuronal input to affective supraspinal sites. Further studies are required to evaluate this theory.

Intraperitoneal administration of a dilute concentration of lactic or acetic acid has been shown to induce abdominal stretching/writhing (visceral pain behavior), an effect associated with a reduction in feeding and hedonic behaviors (pain-depressed behavior). Evaluation of the role of the endocannabinoid system in mediating pain-stimulated and pain-depressed/suppressed responses in this model has revealed that genetic antagonism of CB_1 receptors enhances acid-induced writhing (visceral pain stimulated behavior) and augments acid-induced reductions in feeding (Miller et al., 2011). In contrast, CB_1 receptor agonism using Δ^9-THC and CP55940 dose dependently inhibits acid-stimulated stretching while eliciting either no effect (Miller et al., 2012) or exacerbating (Kwilasz and Negus, 2012) acid-induced depression of feeding and scheduled controlled/intracranial self-stimulation in rats. Thus, under these conditions, potent synthetic cannabinoids such as Δ^9-THC and CP55940 may elicit differential effects on visceral pain (attenuated) and pain-related depressive (exacerbated) behavior. However, the FAAH inhibitor URB597 exhibits a dose-related and CB_1 receptor-mediated decrease in acid-stimulated stretching and suppression of feeding (Miller et al., 2012; Kwilasz et al., 2014). Furthermore, URB597 also elicits a delayed but significant attenuation of acid-induced suppression of intracranial self stimulation, an effect occurring independent of CB_1 or CB_2 mediation (Kwilasz et al., 2014). Taken together, these data indicate a role for CB_1 receptors in mediating acid-induced visceral pain, with a possible common and/or alternative endocannabinoid mechanism mediating the associated anhedonic/depressive-like behavior.

Overall, despite the limited data, evidence suggests a prominent role for the endocannabinoid system in the interaction between depression and pain, although whether the effects are mediated by the same or parallel neuroanatomical pathways remains to be determined.

Mechanisms By Which The Endocannabinoid System May Modulate Depression And Pain Interactions

While the exact mechanism(s) by which the endocannabinoid system may influence emotional and nociceptive processing remains undetermined, this system is known to elicit potent modulatory effects on neurotransmission, neuroendocrine, and inflammatory processes, all known to be altered in both depression and chronic pain. Presented here is an overview of how the endocannabinoid system may modulate affective and pain processing via interacting with these systems.

Neurotransmitters

GABA and Glutamate

GABA- and glutamatergic neurotransmission are well recognized as important mediators in affect and nociceptive processing, and alterations in these systems have been demonstrated in both depression and chronic pain (for review, see Kendell et al., 2005; Rea et al., 2007). There are an increasing number of studies demonstrating that glutamatergic and GABAergic signaling play an important role in mediating the depressive symptoms associated with chronic pain. For example, ketamine, an NMDA receptor antagonist, attenuated depressive-like behavior following spared nerve injury without altering injury-induced hypersensitivity (Wang et al., 2011), while AMPAkines (which augment AMPA receptor function) have been shown to attenuate both pain hypersensitivity and associated depressive-like behavior

in models of chronic inflammatory and neuropathic pain (Le et al., 2014). Furthermore, facilitation of glutamatergic transmission through AMPA receptors in the nucleus accumbens, a brain region involved in reward, resulted in attenuation of depression-like behavior in an animal model of neuropathic pain (Goffer et al., 2013). Despite a recognized role for the GABAergic system in emotional and pain processes, to our knowledge few studies have investigated the role of this system in affect-pain interactions to date. One such study has reported that $GABA_A$ receptor activation in the RVM blocked formalin-induced hyperalgesia produced upon removal from an aversive elevated plus maze (stressor) (Cornelio et al., 2012). In addition, Quintero and colleagues (2011) have also identified that repeated forced swim stress-induced inflammatory hyperalgesia is initiated by decreased and delayed GABA release and $GABA_A$ receptor activation and maintained by increased glutamate release and NMDA activation at the spinal cord level (Suarez-Roca et al., 2008).

CB_1 receptors are expressed at a particularly high density on presynaptic nerve terminals of GABAergic and glutamatergic synapses in cortical and limbic areas of the brain associated with stress, emotional response, and pain modulation (Herkenham et al., 1990; Katona et al., 2001; Domenici et al., 2006; Wittmann et al., 2007). Endocannabinoids have been shown to exert behavioral effects via CB_1 receptor agonism and resultant presynaptic inhibition of GABAergic and glutamatergic transmission (Meng et al., 1998; Millan, 2002) in supraspinal and spinal regions (Ulugol, 2014). In addition, glutamatergic neurotransmission is known to enhance endocannabinoid formation and subsequent CB_1 receptor activation (Galante and Diana, 2004). Thus, complex bidirectional interaction exists between the endocannabinoid-glutamatergic-GABAergic systems. Several studies have demonstrated that CB_1 modulation of GABAergic signaling is important in nociceptive (Manning et al., 2003; Naderi et al., 2005; Pernia-Andrade et al., 2009) and emotional (Haller et al., 2007; Naderi et al., 2008; Rossi et al., 2010; Rey et al., 2012; Reich et al., 2013) processing. Although it would appear intuitive, it is unknown if endocannabinoid modulation of GABA and/or glutamate plays a role in depression-pain interactions. However, we have demonstrated that CB_1 receptors play an important role in mediating analgesia in response to acute stress (contextual fear conditioning) (Finn et al., 2004; Butler et al., 2008) and demonstrated an important role for GABAergic and glutamatergic signaling in the basolateral amygdala in mediating this effect (Rea et al., 2014). Thus, endocannabinoid modulation of GABAergic and glutamatergic tone can mediate stress-pain interactions and therefore may play a prominent role in coexistent psychiatric and pain disorders.

Monoamines

In addition to the treatment of depression, monoamine-based antidepressants are now regarded as first-line therapy for fibromyalgia and neuropathic pain. The monoaminergic system has been proposed as a common neural substrate for depression-pain associations. In accordance, a number of preclinical studies have demonstrated beneficial effects of modulating monoaminergic tone on depression associated with chronic pain and vice versa. For example, recent studies have demonstrated that chronic administration of 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene, which increases serotonergic neurotransmission by inhibiting presynaptic serotonin transport, attenuates mechanical allodynia and depressive-like behavior in an animal model of neuropathic pain (Gai et al., 2014). Furthermore, chronic imipramine treatment reduces depressive-like behavior, but not hyperalgesia, in a rat model of neuropathic pain, effects mediated by increasing the neurotrophin BDNF (Yasuda et al., 2014). In addition, direct administration of a BDNF inducer (4-MC) into the brain attenuated thermal hyperalgesia and depressive-like behavior following nerve injury (Fukuhara et al., 2012; Ishikawa et al., 2014). The spinal serotonergic system has been shown to participate in the thermal hyperalgesia response in an animal model of depression, the olfactory bulbectomized rat (Rodriguez-Gaztelumendi et al., 2014). We have shown recently chronic amitriptyline treatment elicits an antidepressant-like effect and potently attenuates nerve injury-induced mechanical and cold allodynia in the bulbectomy model of depression (Burke et al., 2015). Thus, enhancing monoaminergic tone, and consequently central BDNF expression, modulates pain-depression behaviors.

Several lines of evidence have demonstrated that chronic antidepressant administration modulates endocannabinoid signaling (Hill et al., 2006, 2008b; Mato et al., 2010; Smaga et al., 2014), which underlie at least in part the mechanism by which these pharmacological agents modulate affective and nociceptive processes. Furthermore, endocannabinoid-induced modulation of serotonergic, noradrenergic, and dopaminergic transmission has been thoroughly investigated in several excellent reviews (Haj-Dahmane and Shen, 2011; Melis and Pistis, 2012; Kirilly et al., 2013). CB_1 receptors are highly expressed on serotonergic, noradrenergic, and dopaminergic neurons and play an important role in the regulation of monoaminergic activity. Local and systemic administration of exogenous CB_1 receptor agonists significantly increases serotonin (Bambico et al., 2007), noradrenaline (Jentsch et al., 1997; Oropeza et al., 2005; Page et al., 2007, 2008), and dopamine (Cheer et al., 2004; Solinas et al., 2006) levels in discrete brain regions that mediate emotional and nociceptive processing. Increasing endogenous levels of AEA and 2-AG through systemic administration of FAAH or MAGL inhibitors, respectively, has also been shown to enhance serotonergic and dopaminergic activity (Gobbi et al., 2005; Seif et al., 2011), and FAAH inhibition in the PFC increases serotonergic neuronal firing in the dorsal raphe nucleus (McLaughlin et al., 2012). In addition, endocannabinoids can inhibit the activity of monoamine oxidase (Fisar, 2010), the enzyme responsible for the metabolism of monoamines, which may also contribute to the increasing synaptic availability of the monoamines. Endocannabinoid activation of the CB_1 receptor has been shown to control the function and expression of specific serotonin receptors, namely $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, and $5\text{-}HT_{2C}$, in discrete regions of the CNS (Aso et al., 2009; Moranta et al., 2009; Zavitsanou et al., 2010; Franklin et al., 2013). Furthermore, spinal noradrenergic depletion is associated with compromised analgesic effects of CB_1 agonism on formalin-evoked inflammatory pain (Gutierrez et al., 2003), while CB_1 receptor activation results in attenuation of enhanced serotonergic firing in the dorsal raphe following nerve injury, an effects accompanied by antinociception (Palazzo et al., 2006). Taken together, these data demonstrate that cannabinoids modulate nociceptive tone, in part through modulation of noradrenergic and serotonergic systems. Thus, endocannabinoid-induced enhancement of monoaminergic tone may modulate emotional and nociceptive processes and thus the interaction between depression and pain.

Opioids

Numerous studies have characterized the causative role and therapeutic potential of opioidergic signaling in affective and nociceptive processing (for review, see Maletic and Raison, 2009; Lutz and Kieffer, 2013). Furthermore, alterations in opioid signaling in key brain regions such as the amygdala have

been reported in a chronic pain model that exhibits comorbid anxiety-related behavior (Narita et al., 2006). Acute morphine administration attenuated both mechanical allodynia and anxiety-related behavior in the complete Freund's adjuvant model of inflammatory pain (Parent et al., 2012). A very substantial body of evidence is now available to suggest that the endocannabinoid and opioidergic systems interact in therapeutically beneficial ways. CB_1 and μ-opioid receptors are highly colocalized on neurons in areas of the brain associated with emotional and pain processing such as the caudate putamen, periaqueductal gray, and spinal cord (Rodriguez et al., 2001; Salio et al., 2001; Wilson-Poe et al., 2012). Coadministration of opioids and cannabinoids results in synergistic and bidirectional antinociceptive effects in several animal models (Cichewicz et al., 1999; Cichewicz and McCarthy, 2003; Tham et al., 2005; Roberts et al., 2006; Smith et al., 2007; Wilson et al., 2008; Wilson-Poe et al., 2013). In addition, increasing endocannabinoid tone has been shown to attenuate withdrawal symptoms in morphine-dependent animals (Smith et al., 2007; Wilson et al., 2008; Shahidi and Hasanein, 2011). Interestingly, cross tolerance also exists between these neuromodulatory systems. For example, decreases in the analgesic effects of Δ^9-THC have been identified in morphine-tolerant animals and vice versa (Thorat and Bhargava, 1994). Furthermore, inhibition of opioid signalling (via κ-opioid receptors) attenuates the antidepressant-like effect of rimonabant (CB_1 receptor antagonist/inverse agonist) in the FST (Lockie et al., 2011), and conversely the antidepressant-like effects of κ-opioid receptor antagonism are attenuated by the CB_1 receptor antagonist/inverse agonist AM251 (Braida et al., 2009). Although further studies are required, collectively these findings suggest a regulatory role of the endocannabinoid system on opioid transmission, which may underlie the maintenance of coexistent depression-pain processes.

Neuroendocrine Activity – HPA Axis

Dysregulation of the HPA axis has been implicated in the pathophysiology of both depression and pain disorders for decades (for review, see Bomholt et al., 2004; Vierck, 2006; Maric and Adzic, 2013; Belvederi Murri et al., 2014) and thus has also been proposed as a possible mediator in the depression-pain dyad (for review, see Blackburn-Munro, 2004). Several clinical studies have identified altered HPA axis activity in patients exhibiting symptoms of both depression and pain. For example, a cross-sectional study of patients with advanced breast cancer revealed increasing plasma cortisol levels that positively correlated with symptoms of depression and pain (Thornton et al., 2010). However in patients with fibromyalgia, enhanced cortisol release and dysregulation of HPA function associates with depressive, but not pain, symptoms, implying possible diverging mechanisms for both affective and nociceptive processing in this condition (Wingenfeld et al., 2010). Preclinical evidence of this reciprocity is also evident in an experimental model of gastritis, which is associated with gastrointestinal inflammation, pain, and anxiety- and depressive-like behaviors in rats (Luo et al., 2013). These behavioral alterations are accompanied by dysregulation of the HPA axis, characterized by increased expression of corticotrophin-releasing factor (CRF) mRNA and reduced expression of glucocorticoid receptor in the hypothalamus and increased plasma levels of corticosterone (Luo et al., 2013). Increased expression of CRF has also been reported in the paraventricular nucleus of the hypothalamus and dorsal raphe nucleus of WKY rats and animals preexposed to neonatal maternal separation, respectively (Bravo et al., 2011), two models of depression and associated hyperalgesia. Pharmacological blockade of CRF1 following intraamygdalar infusion of the CRF1 antagonist CP376395 inhibits hyperalgesic responding to colorectal distention in WKY rats, an effect not observed following glucocorticoid receptor or mineralocorticoid receptor antagonism (Johnson et al., 2012). Furthermore, the hyperalgesic visceromotor response to phasic colorectal distension following repeated water avoidance stress has been shown to be attenuated by CRF1 antagonism (Larauche et al., 2008). In addition, systemic or intraamygdalar injection of the CRF1 receptor antagonist NBI27914 blocks anxiety-related and nocifensive behavior in a rat model of arthritis (Ji et al., 2007). Thus, the CRF-HPA stress axis has been shown to play a key role in affective and/or nociceptive processing.

Several lines of evidence now support an important role for the endocannabinoid system as a modulator of HPA axis function and vice versa (for review, see Finn, 2010; Riebe and Wotjak, 2011; Hill and Tasker, 2012). The majority of evidence collated to date would suggest that basal HPA activity is under tonic inhibitory control by CB_1 receptors. This has been shown in numerous reports where genetic deletion or pharmacological blockade of the CB_1 receptor in vivo enhances expression of CRF and reduces glucocorticoid receptor expression in the hypothalamus and pituitary gland, respectively (Cota et al., 2007), and increases circulating levels of corticosterone and adrenocorticotropic hormone (Barna et al., 2004; Cota et al., 2007; Steiner et al., 2008). In addition, stress-induced increases in CRF expression in the paraventricular nucleus of the hypothalamus and the basolateral amygdala, as well as corticosterone secretion, are effectively blocked by pharmacological enhancement of endocannabinoid levels (Patel et al., 2004; Hill et al., 2009a; Bedse et al., 2014; Roberts et al., 2014), thus implying a role for endocannabinoid-CB_1 receptor signaling in diminished hyperactivity of the HPA axis. Furthermore, recent evidence has shown that CRF1 activation in the amygdala induces FAAH and reduces AEA levels, an effect associated with anxiety-related behavior (Gray et al., 2015). Given the important role of the amygdala in affective modulation of pain, it is possible that CRF-mediated FAAH activation in this region may also modulate nociceptive possessing and associated emotional alterations. While there have been a few studies examining endocannabinoid-HPA axis effects in mediating the effects of the stress response (Hill et al., 2011; Roberts et al., 2014), to date no study has investigated if cannabinoid-mediated alterations of the HPA axis underlie alterations in nociceptive and/or affective behavior observed in depression-pain comorbidity.

Neuro-Inflammatory Processes

Increasing evidence indicates a potent and prominent interaction between inflammation, depression, and pain (for review, see Walker et al., 2014). For instance, there is a high prevalence of depression among patients with inflammatory pain disorders such as fibromyalgia, arthritis, and irritable bowel disorder (Kappelman et al., 2014; Scheidt et al., 2014; Lin et al., 2015). In addition, patients receiving cytokine therapy for specific cancers and malignancies also develop depressive and/or painful symptomatology (Capuron and Ravaud, 1999; Capuron et al., 2001; Nogueira et al., 2012). Furthermore, increases in serum and cerebrospinal fluid levels of proinflammatory cytokines have been widely reported in both depression (Tuglu et al., 2003; Knuth et al., 2014; Bay-Richter et al., 2015) and pain conditions (Koch et al., 2007; Ludwig et al., 2008; Kadetoff et al., 2012). Inflammatory processes have also been shown to underlie the interaction between

depression and pain in several animal models. For instance, increased expression of proinflammatory cytokines, concomitant with depressive-like behavior, has been identified in animal models of inflammatory (Kim et al., 2012; Maciel et al., 2013) and neuropathic (Norman et al., 2010; Burke et al., 2014; Dellarole et al., 2014; Zhou et al., 2015) pain. The innate inflammatory cascade has been shown to increase glutamate neurotransmission, central sensitization, and excitotoxicity, reduce BDNF and neurogenesis, and activate neurodegenerative cascades, events observed in both depression and pain conditions (for review, see Dantzer et al., 2011; Maes et al., 2011; Song and Wang, 2011; Zunszain et al., 2013; Walker et al., 2014).

Over the past decade, a wealth of data has demonstrated an important role for the endocannabinoid system in modulating innate immune function and inflammatory processes (for review, see Alhouayek and Muccioli, 2012; Zajkowska et al., 2014; Henry et al., 2015). Interactions between the endocannabinoid system and inflammatory mediators has been shown to influence synaptic transmission and neuronal function (Rossi et al., 2014). Spinal cord injury has been shown to be associated with increased coexpression of CB_1 receptors with chemokines CCL2, CCL3, and/or CCR2 in the hippocampus, thalamus, and periaqueductal grey, areas associated with affective pain responding (Knerlich-Lukoschus et al., 2011), and studies have also demonstrated that CB_1-chemokine interactions in the periaqueductal grey can modulate nociceptive responding (Benamar et al., 2008). Pharmacological enhancement of endocannabinoid tone also modulates inflammatory effects in vivo. For example, the FAAH inhibitor URB597 and the MAGL inhibitor JZL184 attenuate inflammation-induced astrocyte and microglial activation (Katz et al., 2015) and neuroinflammatory processes (Kerr et al., 2012, 2013; Henry et al., 2014). Furthermore, Zoppi and colleagues (2011, 2014) have demonstrated that pharmacological activation of CB_1 or CB_2 receptors attenuates, while genetic deletion of these receptors augments, repeated stress-induced proinflammatory responses in the frontal cortex. In addition, several studies have demonstrated that the analgesic effects of cannabinoids in chronic inflammatory and neuropathic pain are at least partially mediated by modulation of inflammatory responses (Burgos et al., 2012; Wilkerson et al., 2012; Burston et al., 2013; Lu et al., 2015). While there are no studies to date investigating if cannabinoid modulation of inflammatory processes underlies coexistent depressive and pain behavior, the above findings suggest a potential role for cannabinoid-mediated immunomodulation in the pathogenesis and treatment of co-occurring depression and pain.

Conclusion and Future Directions

This review has provided an overview of the clinical and preclinical evidence supporting an association between depression and pain and vice versa. While a number of neural substrates have been proposed to underlie this association, this review provides a synthesis of the data supporting the contention that comorbid depression and pain may be mediated at least in part via dysregulation of the endocannabinoid system. Targeting the endocannabinoid system for therapeutic benefit has been an ever-expanding area of research with more than 150 clinical trials during the past decade evaluating the effects of cannabinoids in pain and psychiatric disorders (International Clinical Trials Registry Platform). While no study to date has specifically evaluated the effects of cannabinoids on depression-pain comorbidity, several have examined effects on mood and quality of life in patients receiving cannabinoid-based pharmaceuticals for analgesic purposes (Maida et al., 2008; Skrabek et al., 2008; Weber et al., 2009; Cameron et al., 2014), providing a basis for further study in this area. However, many of these cannabinoids are potent CB_1 receptor agonists (Δ^9-THC derivatives), an effect that may limit their usefulness in psychiatric conditions due to the associated adverse CNS effects. Cannabidiol has been shown to limit the adverse CNS effects associated with CB_1 receptor agonists, and Sativex (1:1 Δ^9-THC:cannabidiol) has been shown to reduce chronic pain and improve mood (Selvarajah et al., 2010; Vermersch, 2011). Thus, combination therapy may be a beneficial treatment strategy for depression-pain comorbidity. As highlighted throughout this review, modulation of endogenous cannabinoid tone provides an alternative to direct CB_1 receptor agonism and although still in the early stages of clinical investigation, FAAH inhibitors such as PF-04457845 have demonstrated safety and tolerability in patients, although no effect on pain associated with osteoarthritis was reported (Huggins et al., 2012). However, this inhibitor is currently under clinical investigation for treatment of cannabis withdrawal, PTSD, and Tourette syndrome (International Clinical Trials Registry Platform), the results from which will provide important clinical data on the effect of FAAH inhibition on affective responding. Further clinical studies will provide greater insight into alterations and the role of the endocannabinoid system in the association between depression and pain.

Preclinical models that encapsulate the clinical scenario are particularly useful in gaining greater understanding of the neurobiology underlying depression-pain interactions. This review has presented the evidence to date demonstrating alterations in various components of the endocannabinoid system in models of depression-pain comorbidity and highlighted a particular role for AEA and CB_1 receptors in mediating and modulating the affective and nociceptive processes in these models. However, research in this area is still in its infancy, and this review highlights the gaps in the knowledge and outstanding questions that remain to be addressed. For example, there have been limited data examining the role of other components of the endocannabinoid system on depression-pain interactions (2-AG, CB_2, peroxisome proliferator-activated receptors, etc.), whether the endocannabinoid modulation of affect and nociception occur through the same or parallel pathways, and the mechanism by which the endocannabinoid system may mediate its effects (neurotransmitters, HPA axis, inflammation, or a combination). Furthermore, it is unknown if the role of the endocannabinoid system in chronic pain associated with depression is the same or different from altered affective processing associated with chronic pain conditions. Such studies are essential if we are to move towards a more comprehensive understanding of the neurobiology underlying the association between these pain and depression and fully explore the potential clinical efficacy of targeting the endocannabinoid system for resolution of these comorbid conditions.

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Statement of Interest

None.

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