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Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal

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Abstract

Withdrawal from opiates, such as heroin or oral narcotics, is characterized by a host of aversive physical and emotional symptoms. High rates of relapse and limited treatment success rates for opiate addiction have prompted a search for new approaches. For many opiate addicts, achieving abstinence may be further complicated by poly-drug use and co-morbid mental disorders. Research over the past decade has shed light on the influence of endocannabinoids on the opioid system. Evidence from both animal and clinical studies point towards an interaction between these two systems, and suggest that targeting the endocannabinoid system may provide novel interventions for managing opiate dependence and withdrawal. This review will summarize the literature surrounding the molecular effects of cannabinoids and opioids system on the locus coeruleus-norepinephrine system, a key circuit implicated in the negative sequelae of opiate addiction. A consideration of the trends and effects of marijuana use in those seeking treatment to abstain from opiates in the clinical setting will also be presented. In summary, the present review details how cannabinoid-opioid interactions may inform novel interventions in management of opiate dependence and withdrawal.

1) Opioid Addiction: A Persistent Societal Problem

a. Background

Overall, illicit drug abuse in the United States exceeded $180 billion in 2008 according to National Institutes of Health. Abuse of heroin and prescription opioids have long constituted a significant economic burden to society both through the direct and indirect consequences of illicit opioid use. These costs include not only direct medical expenses, but also the costs of criminal activities associated with drug acquisition, social welfare, secondary medical issues associated with high-risk needle sharing, and productivity losses. In 1996, the cumulative economic burden of heroin addiction in the United States was estimated to be $21.9 billion(Mark et al., 2001). In 2001, illicit use of prescription opioids cost the United

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States approximately $8.6 billion, and this number continues to rise (Birnbaum et al., 2006, Gilson and Kreis, 2009, Strassels, 2009).

Intravenous heroin use experienced a steady climb through the early 1980's in the United States, until rates began to decline concurrent with the implementation of programs designed to increase awareness of the risks associated with intravenous drug use and needle sharing. However, since the mid-1990's heroin use has experienced a resurgence, particularly among younger populations. In 2004, an estimated 3.7 million people in the United States had reported using heroin at some point in their lifetime according to data collected by the National Institute on Drug Abuse. The 2008 National Survey on Drug Use and Health determined that the number of heroin users over the age of 12 in the United States had increased dramatically from 153,000 in 2007 to 213,000 in 2008. Unlike prior surges in heroin use that were primarily characterized by injection drug use, recent climbs in heroin use rates are due to significant increases in inhaled or snorted heroin. Heroin purity increased dramatically during the 1990's and has remained stable(OAS, 2005). Meanwhile, the cost of heroin has decreased and is now less expensive relative to other opioid alternatives, potentially underlying the trends in increased inhalation drug use(OAS, 1998). The high abuse liability of heroin was demonstrated in a 2004 study of drug use, which found that 67% of those that used heroin also met the criteria for abuse or dependence, a statistic markedly higher than that for other drugs of abuse such as cocaine, marijuana, or sedatives(OAS). In 2008, 341,000 individuals received treatment for heroin dependence(OAS, 2009) and with recent increases in use, this number is likely to continue to climb.

b. Non-Medical Use of Prescription Opioids

Heroin use, while extremely problematic, is restricted to a very small percentage of the population. However, non-medical use of prescription opioids is now becoming more prevalent with rates of use rapidly increasing. The misuse or abuse of prescription drugs occurs when a person takes a prescription drug that was not prescribed or taken in one dose or for reasons other than those prescribed. Abuse of prescription drugs can produce serious health effects, including addiction. The classes of prescription drugs that are commonly abused include oral narcotics such as hydrocodone (Vicodin ®), oxycodone (OxyContin ®), propoxyphene (Darvon ®), hydromorphone (Dilaudid ®), meperidine (Demerol ®) and diphenoxylate (Lomotil ®) and their non-medical use has increased dramatically in recent years. For example, in 1990, the number of individuals initiating abuse of prescription opioids was 573,000. By the year 2000, the number had risen to over 2.5 million according to the National Institutes of Health. A 2009 nationwide study reported that 6.2 million individuals were recent non-medical users of prescription opioids(OAS, 2009). Among high school seniors, as many as 1 in 10 used prescription opioids for non-medical purposes in 2009. For the first time, the number of individuals initiating prescription opioid use nearly equaled that of marijuana; a previously unprecedented and alarming finding. Concurrently, emergency department visits due to complications from non-medical use of hydrocodone and oxycodone rose 170% and 450% respectively from 1994–2002. Furthermore, opioid-related deaths rose by more than 300% between 1999–2006 (OAS, 2009).

II. The Clinical Opioid Withdrawal Syndrome & Underlying Brain Circuitry

a. Clinical presentation and management

Abstinence following chronic exposure to opiates is accompanied by a pronounced syndrome of aversive physical and emotional symptoms. Characteristic signs of opiate withdrawal include yawning, rhinorrhea, perspiration, dilated pupils, anxiety and restlessness, nausea and vomiting, diarrhea, increased heart rate or blood pressure, as well as

a host of flu-like symptoms such as chills, joint and muscle aches, and increased body temperature(Jasinski, 1981, Gossop, 1988, Farrell, 1994, Wesson and Ling, 2003). In opiate-dependent individuals, the experience of a pronounced and prolonged withdrawal syndrome often contributes to renewed illicit drug use and less-than-favorable treatment prognoses.

Pharmacotherapeutics designed to attenuate the severity of these opiate withdrawal signs can be used to promote improved outcome in the critical early phases of treatment. Currently, the pharmacotherapeutic options for opioid dependence and withdrawal are primarily designed around the principles of maintenance therapy and/or detoxification. Agonist replacement or maintenance therapy involves substitution of illicit opioid use with long-acting opioid-receptor agonists in a carefully controlled manner. Ideal agonist replacement drugs often bind to opioid receptors with greater affinity and are metabolized more slowly than commonly abused illicit opioids. Alternatively, opioid detoxification employs opioid receptor antagonists that provide potent and high-affinity blockade of mu-opioid receptor (MOR). These compounds work by inducing withdrawal, often through the displacement of illicit opioids from receptor binding sites in the nervous system.

To assist with opioid detoxification and the associated withdrawal syndrome, alpha-2 adrenergic receptor agonists are also used to address the noradrenergic hyperactivity that is a hallmark of opioid withdrawal. Clonidine and lofexidine are centrally-acting α-2 adrenergic receptor agonists used during rapid opioid detoxification to regulate noradrenergic hyperactivity associated with opioid withdrawal. These agents are often co-administered with opioid receptor antagonists during detoxification. Clonidine rapidly and effectively reduces withdrawal symptoms, but can cause postural hypotension through its actions on noradrenergic control of cardiovascular function(Gossop, 1988). Lofexidine, which works similarly to clonidine but involves lessened risk of hypotension, has shown greater efficacy than clonidine in recent studies(Strang et al., 1999, Gerra et al., 2001, Meader, 2010). The activity of these agents is heavily reliant on their activity within a key noradrenergic nucleus within the brain- the locus coeruleus (LC).

b. Noradrenergic circuitry

The LC is located in the anterior pons of the brainstem, near the fourth ventricle. This nucleus provides the majority of noradrenergic input to the central nervous system, and is highly interconnected with many different brain regions, allowing for the regulation of cognition, pain, emotional state, anxiety, arousal, and stress(Aston-Jones and Bloom, 1981, Aston-Jones et al., 1986, Nestler et al., 1999, Carrasco and Van de Kar, 2003, Dunn et al., 2004). The widespread downstream effects of LC neurotransmission occur as a result of the diverse network of projections sent to and from this nucleus to the entire neuraxis. The LC is a key anatomical locus where opioid and stress signaling intersect. Many of the neurons projecting from the nucleus paragigantocellularis (PGi) and nucleus prepositus hypoglossi (PrH) provide enkephalin to the LC(Aston-Jones et al., 1986, Aston-Jones et al., 1991), while corticotropin releasing factor (CRF) innervation arises predominantly from the PGi, paraventricular nucleus of the hypothalamus (PVN), and peri-coerulear region(Valentino et al., 1993, Valentino et al., 1998a). The LC is extremely sensitive to opioid and stress peptides delivered by afferent fibers due to the high density of opioid and CRF receptors (Pert et al., 1976, Valentino et al., 1983, Aston-Jones et al., 1986, Tempel and Zukin, 1987, Ding et al., 1996, Van Bockstaele et al., 1996a, Reyes et al., 2007). The kappa-opioid receptor (KOR) and delta-opioid receptor (DOR) have a prominent pre-synaptic distribution in the LC and are poised to auto-regulate neurotransmitter release from LC afferents(Van Bockstaele et al., 1997, Kreibich et al., 2008, Reyes et al., 2009a) (Kreibich et al., 2008). The mu-opioid receptor (MOR) has a dense post-synaptic distribution along the plasmalemma of somata and dendrites of LC neurons(Van Bockstaele et al., 1996a, Van

Bockstaele et al., 1996b). The MOR-mediated sensitivity and response of this region to opioid exposure has been extensively studied and characterized.

c. Molecular Expression of Opioid Dependence and Withdrawal in LC Circuitry

MOR is a G-protein coupled receptor that typically signals through $G_{i/o}$ alpha-subunit proteins to inhibit the activity of adenylyl cyclase (AC) I and VIII, thereby reducing cyclic adenosine monophosphate (cAMP) production, impacting Na^+ current and neuronal excitability(Childers et al., 1992, Dhawan et al., 1996). Additionally, opioids also inhibit the LC by coupling opioid receptor activation to G-protein-gated inwardly rectifying K^+ (GIRK) ion channels(Christie et al., 1987, North et al., 1987, Nestler, 1992, 2001). Direct effects of opioid exposure can include receptor desensitization and internalization via a clathrin-mediated mechanism(Van Bockstaele and Commons, 2001, Van Bockstaele et al., 2001, Alvarez et al., 2002, Dang and Williams, 2005, Johnson et al., 2005, Arttamangkul et al., 2006, Gintzler and Chakrabarti, 2006). In this manner, MOR activation by opioids has an acutely inhibitory effect in the LC, resulting in sedation, hypolocomotion, analgesia, and respiratory depression.

Following repeated exposure to opioids, a number of cellular adaptations occur within this region that significantly impact the development of opioid dependence and manifestation of opioid withdrawal. Suppression of AC-I and AC-VIII by opioid exposure leads to decreased cAMP levels and protein kinase-A (PKA) activity, and decreased phosphorylation of cAMP response element binding protein (CREB), a downstream effector of PKA. By binding to regulatory DNA sequences called cAMP response elements (CREs), CREB is able to alter the expression of key proteins in the cAMP pathway. Opioid exposure alters the phosphorylation level of CREB, thereby regulating the transcriptional activation of CREB target genes. These transcriptional changes may include increased expression of AC-VIII, PKA catalytic and regulatory subunits, CREB, and tyrosine hydroxylase (the rate-limiting enzyme in norepinephrine synthesis). As an end result of these adaptations, the cAMP pathway is upregulated and the electrical excitability in the LC increases (Widnell et al., 1994, Lane-Ladd et al., 1997, Nestler and Aghajanian, 1997, Boundy et al., 1998, Coven et al., 1998, Nestler, 2001).

Through its wide array of projections throughout the brain, hyperactivity in the LC during opiate withdrawal has the potential to impact signaling in a number of brain regions, primarily in the frontal cortex to which it provides the sole noradrenergic input [reviewed (Valentino and Aston-Jones, 2000, Berridge and Waterhouse, 2003, Van Bockstaele et al., 2010)]. Alterations in LC activity have been implicated in the somatic expression of withdrawal (Taylor et al., 1988, Rasmussen et al., 1990, Koob et al., 1992, Maldonado and Koob, 1993, Funada et al., 1994, Maldonado, 1997), and it has been shown that these effects are mediated by the excitatory input from the nucleus paragigantocellularis (PGi) (Rasmussen and Aghajanian, 1989, Maldonado, 1997, Van Bockstaele et al., 2000, Van Bockstaele et al., 2001, Johnson et al., 2002).

Upon the removal of opioids from the system, a surge in noradrenergic activity from the locus coeruleus contributes significantly to the somatic expression of opioid withdrawal (Crawley et al., 1979, Swann et al., 1982, Van Bockstaele et al., 2008). Within noradrenergic targets of the LC, opiate withdrawal-mediated LC disturbances can be appreciated in terms of increased tyrosine hydroxylase, c-Fos and FosB expression, along with enhanced activation (phosphorylation) of cyclic adenosine monophosphate (c-AMP) pathway members (Stornetta et al., 1993, Nestler et al., 1994, Maldonado et al., 1995, Nestler and Aghajanian, 1997, Nestler, 2001, Van Bockstaele et al., 2001, Maldonado, 2003). Both intrinsic and extrinsic factors to the LC contribute to the withdrawal phenomenon. The cAMP-related cellular adaptations that occur in response to chronic

opioid exposure cause enhanced excitability in LC neurons. When coupled with the removal of inhibitory opioid input upon withdrawal or detoxification, this combination results in the dysregulation of the LC-noradrenergic circuit (Nestler et al., 1994, Nestler, 2001). In addition to upregulated cAMP pathway activity in the LC, excitatory amino acid influx to the LC from its afferents also contributes to the molecular expression of opioid withdrawal (Akaoka and Aston-Jones, 1991, Aghajanian et al., 1994, Maldonado, 1997, Van Bockstaele et al., 2001). Common therapeutic approaches employed in the management of opioid withdrawal are targeted to adrenergic receptors with the intent of counteracting cellular hyperactivity and restoring LC homeostasis.

Therapeutic agents targeting the brain's noradrenergic circuitry have demonstrated clinical efficacy in attenuating the noradrenergic hyperactivity that is observed during opiate withdrawal (Gold et al., 1979, Gossop, 1988, Gold, 1993, Gowing et al., 2004). However, in some individuals, the use of alpha-2 adrenergic receptor agonists is limited by the presence of side effects such as hypotension, sedation, and cognitive impairment, or by incomplete abolition of withdrawal symptoms (Gossop, 1988, Gerra et al., 2001, Lobmaier et al., 2010). It remains important to investigate other receptor systems that interact with the opioid system in noradrenergic brain regions and may serve as potential therapeutic targets.

III. Cannabinoid Modulation of Noradrenergic Circuitry

a. The endocannabinoid (EC) system

Through significant advances in our understanding of the cannabinoid system in recent years, we now understand that the endogenous cannabinoid system—or endocannabinoid system—is the primary regulator of cannabinoid functions in the brain. The endocannabinoid (EC) system has been implicated in a variety of physiological functions due to abundant expression of its receptors and endogenous ligands in the central nervous system(Herkenham et al., 1991, Mackie, 2005b, 2008). The EC consists of receptors, ligands and enzymes responsible for their biosynthesis and degradation. Endocannabinoids are lipophilic arachidonic acid derivatives that are released in an activity dependent fashion from the postsynaptic cell(Piomelli et al., 1998, Piomelli, 2003, Di Marzo et al., 2005, Piomelli, 2005, Basavarajappa, 2007). Two major endocannabinoids have been identified: anandamide(Devane et al., 1992, Di Marzo et al., 1994) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995, Sugiura et al., 1995, Stella et al., 1997, Mechoulam et al., 1998, Martin et al., 1999). Endocannabinoids control emotional reactivity, motivated behaviors and energy homeostasis primarily by targeting brain CB1 type 1 receptors (CB1r) (Mechoulam et al., 1998, Giuffrida et al., 2001, Fride, 2002, Kreitzer and Regehr, 2002, Wilson and Nicoll, 2002, Piomelli, 2005, Witkin et al., 2005, Mackie, 2008, Steiner et al., 2008, Steiner and Wotjak, 2008). The CB1r is one of the most plentiful G-protein coupled receptors within the brain, and cannabinoid signaling through this receptor mediates a wide variety of peripheral and central processes (Howlett et al., 1990, Howlett et al., 2002, Freund et al., 2003, Szabo and Schlicker, 2005, Demuth and Molleman, 2006).

b. The EC, noradrenergic circuitry and stress

The EC and noradrenergic systems are significantly and dynamically impacted by stress (Hill and McEwen, Cassens et al., 1980, Flugge et al., 2004, Gorzalka et al., 2008, Shinba et al., 2010) and noradrenergic transmission is responsible for cannabinoid-induced activation of the HPA axis(McLaughlin et al., 2009). Under conditions of acute stress, NE is increased centrally and peripherally(Cassens et al., 1980, Abercrombie and Jacobs, 1987, Page and Valentino, 1994, Valentino et al., 1998b, Ferry et al., 1999, Nestler et al., 1999, Sands et al., 2000) while the EC system tonically constrains activation of neural circuits, including the hypothalamic-pituitary-adrenal (HPA) axis(Gorzalka et al., 2008, Steiner and Wotjak,

2008). However, disrupted noradrenergic and EC signaling is associated with an inability to adapt to chronic stress(Nestler et al., 1999, Wong et al., 2000, Flugge et al., 2004, Hill and Gorzalka, 2004, Gorzalka et al., 2008, Hill et al., 2008). We recently demonstrated that pre-treatment with a cannabinoid receptor agonist diminishes acute stress-induced noradrenergic transmission in the mPFC(Reyes et al., 2012). Cannabinoid pre-treatment also resulted in a decrease in climbing during a single exposure to swim, an arousal-related behavior that has been attributed to availability of NE(Detke et al., 1995). Furthermore, we tested the effect of acute stress on 2-AR-cannabinoid interactions in rats(Reyes et al., 2012). Chronic CB1r stimulation with WIN 55,212-2 in slices from unstressed animals desensitized the cortical 2-AR response, similar to the desensitization produced by acute WIN 55,212-2 pretreatment. However, when animals were exposed to chronic WIN 55,212-2 and then given a forced swim stress before brain slices were prepared for electrophysiology, the cortical 2-AR response did not desensitize and is similar in magnitude to subjects that are neither stressed nor exposed to CB1r stimulation. These findings indicate that stress sensitizes the cortical 2-AR response, making it resistant to desensitization by chronic activation of CB1rs. These data reveal the stress-dependent nature of cannabinoid interactions and implicate pre- and postsynaptic ARs. However, although information regarding interactions between the two systems is emerging, there remain gaps in our knowledge regarding how cannabinoids modulate noradrenergic circuitry under different physiological conditions.

Anatomical and electrophysiological studies within the coeruleo-cortical pathway demonstrate cannabinoid sensitivity within noradrenergic cells (Mendiguren and Pineda, 2004, Oropeza et al., 2005, Mendiguren and Pineda, 2006b, a, Muntoni et al., 2006, Mendiguren and Pineda, 2007, Oropeza et al., 2007, Page et al., 2007, Scavone et al., 2010). Convergent lines of evidence (Muntoni, 2001, Mendiguren and Pineda, 2006a, Muntoni et al., 2006) have demonstrated an interaction between the cannabinoid and noradrenergic systems in areas such as the mPFC(Oropeza et al., 2005, Oropeza et al., 2007, Page et al., 2007, Page et al., 2008), nucleus accumbens (Acb)(Carvalho and Van Bockstaele, Carvalho et al., 2010a, Carvalho et al., 2010b), locus coeruleus (LC)(Oropeza et al., 2005, Scavone et al., 2010) and the nucleus of the solitary tract (NTS)(Jelsing et al., 2009, Carvalho et al., 2010a, Carvalho et al., 2010b). Recent anatomical evidence demonstrates the presence of cannabinoid receptors in noradrenergic cells within the NAc and NTS (Carvalho et al., 2010a), frontal cortex (Oropeza et al., 2007, Page et al., 2008, Reyes et al., 2009b), and LC (Scavone et al., 2010).

While the interactions between the noradrenergic and opioid systems have been well characterized in addiction [reviewed in (Van Bockstaele et al., 2001, Berridge and Waterhouse, 2003, Weinshenker and Schroeder, 2007, Aston-Jones and Kalivas, 2008, Sara, 2009, Van Bockstaele et al., 2010)], the field of cannabinoid-opioid interactions in noradrenergic cells is relatively in its infancy. However, increasing numbers of groups have begun to uncover and probe the close interaction between the cannabinoid and opioid systems in the brain and periphery [reviewed in(Manzanares et al., 1999, Corchero et al., 2004a, Fattore et al., 2004, Fattore et al., 2005a, Vigano et al., 2005a, Welch, 2009, Parolaro et al., 2010)].

IV. Cannabinoid-Opioid Interactions

Opioid and cannabinoid receptors are major targets for many drugs of abuse and widely-used analgesics. These receptor systems are known to mediate common signaling pathways central to clinical issues of tolerance, dependence and addiction (Manzanares et al., 1999, Pasternak, 2005, Demuth and Molleman, 2006). Drugs that target both the CB1r and MOR systems possess shared pharmacological profiles. Agonists of both receptor types have been shown to cause antinociception, sedation, hypotension, motor depression, and drug reward/

reinforcement (Manzanares et al., 1999, Massi et al., 2001, Maldonado and Valverde, 2003, Corchero et al., 2004a). Cannabinoids may be able to modulate opioid function at a number of different levels within the cell, ranging from direct receptor associations, to alterations in endogenous peptide release, or to post-receptor interactions via shared signal transduction pathways. Evidence of these interactions can be observed through the various studies demonstrating cross-tolerance, mutual potentiation, and receptor cross-talk (Manzanares et al., 1999, Cichewicz and McCarthy, 2003, Maldonado and Valverde, 2003, Corchero et al., 2004a, Vigano et al., 2005a, Roberts et al., 2006, Cox et al., 2007, Barta et al., 2009, Welch, 2009, Parolaro et al., 2010). Importantly, drugs that target the cannabinoid system often seem to affect the opioid system in tandem. Individual modulation of CB1r or MOR has been shown to alter indices of noradrenergic activity (Nestler, 1993, Nestler et al., 1999, Oropeza et al., 2005, Szabo and Schlicker, 2005). Since the LC and associated noradrenergic circuitry are critical sites of dysfunction during opioid addiction and withdrawal, it is particularly important to develop a comprehensive understanding of both the anatomical substrates and biochemical mechanisms through which cannabinoids may be used to specifically and effectively target the opioid system in this region.

a. Anatomical Considerations

Techniques used to discern the distribution of cannabinoid and opioid receptors and their endogenous ligands have provided valuable information pertaining to the interactions between these systems. Using immunohistochemical and immuno-electron microscopic techniques, anatomical data have revealed potential sites and systems where cannabinoids may be used to target the opioid system. Morphological substrates for cannabinoid-opioid interactions have been demonstrated through CB1r and MOR co-localization in multiple brain regions. These receptors co-localize within the dorsal horn of the spinal cord (Salio et al., 2001). In the nucleus accumbens (NAc), a region critical to the reward circuitry, CB1r and MOR are both localized within neurons and in synaptically-linked pairs of cells (Pickel et al., 2004). Additionally, an ultrastructural study of the caudate-putamen revealed CB1r and MOR labeling targeted to specific patches of post-synaptic neurons with approximately 50% of all CB1r-positive dendrites containing the MOR (Rodriguez et al., 2001). However, only recently has the field begun to generate evidence for cannabinoid-opioid interactions within noradrenergic loci within the brain.

The MOR is abundant within many of the noradrenergic brain regions responsible for mediating the adaptations that occur in response to opiate exposure and in the precipitation of opiate withdrawal (Tempel and Zukin, 1987, Maldonado et al., 1992, Mansour et al., 1995, Cheng et al., 1996, Ding et al., 1996, Moyse et al., 1997, Pickel and Colago, 1999 {Maldonado, 1992 #664). Recent anatomical and functional evidence demonstrates the presence of cannabinoid receptors in noradrenergic cells within the NAc and NTS (Carvalho et al., 2010a, Carvalho et al., 2010b), frontal cortex (Oropeza et al., 2007, Page et al., 2008, Reyes et al., 2009b), and LC (Scavone et al., 2010). Data from electrophysiological recordings in the locus coeruleus also support these anatomical findings, providing evidence of cannabinoid sensitivity in this opioid-sensitive nucleus (Mendiguren and Pineda, 2006b, a). Physiological data following local infusions of cannabinoids on to the opioidergic LC provide additional evidence of local cannabinoid effects (Muntoni et al., 2006). CB1r is expressed in the terminals of noradrenergic projections from the opioid-sensitive LC to the frontal cortex (Oropeza et al., 2007), suggesting that CB1r may be poised to modulate the norepinephrine release that occurs as a result of opioid dependence or withdrawal. Alternatively, indirect mechanisms involving GABA interneurons cannot be ruled out (Reyes et al, 2012). There is also evidence of CB1r and MOR co-localization in shared post-synaptic cellular compartments of the neurons that give rise to these projections (Scavone et al., 2010).

Co-localization of CB1r and MOR within noradrenergic brain regions is particularly noteworthy given the growing body of evidence that is strongly suggestive of heterodimerization and/or closely-associated CB1r-MOR signaling complexes *in vitro* and *in vivo* (Rios et al., 2001, Mackie, 2005a, Rios et al., 2006, Schoffelmeer et al., 2006, Hojo et al., 2008). Additionally, recent studies report increased abundance of CB1r-heterodimers and opioid receptor-heterodimers in response to chronic drug exposure or repeated receptor stimulation (Kearn et al., 2005, Gupta et al., 2010). Potential implications of GPCR heterodimerization include altered subcellular localization or ligand binding properties, in addition to changes in signal transduction (Rios et al., 2001, Terrillon and Bouvier, 2004).

b. Cannabinoid-opioid system cross-talk

Downstream evidence of cannabinoid modulation of the opioid system can be observed through the many accounts in the literature of cannabinoid-opioid synergy, cross-agonism, cross-antagonism, and cross-tolerance (Manzanares et al., 1999, Lichtman et al., 2001, Navarro et al., 2001, Valverde et al., 2001, De Vries et al., 2003, Cichewicz, 2004, Fattore et al., 2005b, Fattore et al., 2007b). Numerous studies have revealed synergistic effects of cannabinoid-opioid pairings such as CP55,940 & morphine (Welch and Stevens, 1992, Tham et al., 2005), delta-9-tetrahydrocannabinol (Δ^9-THC, psychoactive component of marijuana) & morphine in an arthritis model (Cox et al., 2007), and Δ^9-THC & morphine in humans (Roberts et al., 2006). Moreover, combined sub-analgesic doses of Δ^9-THC and morphine possessed synergistic antinociceptive properties while circumventing the development of tolerance inherent to chronic morphine exposure (Cichewicz et al., 1999, Cichewicz and McCarthy, 2003, Cichewicz, 2004, Smith et al., 2007). Cannabinoids have also been shown to exert cross-antagonism within the opioid system (Vigano et al., 2005a). Similar studies have implicated the endogenous cannabinoid system in opioid dependence, as inhibition of cannabinoid receptor signaling with the cannabinoid receptor antagonist SR141716A during chronic opioid exposure reduced opioid withdrawal signs (Rubino et al., 2000, Mas-Nieto et al., 2001). Additionally, cross-sensitization to the behavioral effects of cannabinoids and opioids have also been demonstrated (Cadoni et al., 2001).

The mechanisms through which cannabinoids are able to modulate the opioid system may be through alterations in the level of endogenous opioids or their receptors, or via changes in G-protein mediated signaling through the opioid receptors or MOR-CB1r complexes (Figure 1). Numerous studies have reported changes in the levels of endogenous opioids following cannabinoid administration, suggesting a regulatory role for CB1r in endogenous opioid release (Corchero et al., 1997a, Manzanares et al., 1998, Corchero et al., 1999, Valverde et al., 2001). For instance, repeated Δ^9-THC treatments increased the expression of endogenous opioid peptides in the rat spinal cord (Corchero et al., 1997a). Alternatively, the direct interaction of CB1r and MOR has also been postulated as the mechanism for cannabinoid modulation of the MOR system. Resonance energy transfer studies reveal close associations between CB1r and MOR, while anatomical studies display the co-localization of these receptors in shared cellular compartments (Rodriguez et al., 2001, Salio et al., 2001, Pickel et al., 2004). Devi's group has proposed that cannabinoid and opioid receptors exist as heterodimeric systems that physically interact to integrate independent signal pathways (Rios et al., 2006). These receptor systems may also interact at the level of their intracellular signaling molecules. In addition to baseline receptor similarities, several studies have revealed cannabinoid-induced changes in MOR-dependent G-protein activation through GTPγS binding assays (Corchero et al., 1999, Vigano et al., 2005b, Ellgren et al., 2006, Rios et al., 2006). Cannabinoid-opioid crosstalk can also be observed through receptor expression levels, as repeated administration of Δ^9-THC regulates MOR density in a time and region-dependent manner (Corchero et al., 2004b). Although the functional relationship

between opioid and cannabinoid systems is becoming better established, the specific mechanisms of their interaction in the LC and associated circuits remain to be elucidated.

Shifts in the subcellular distribution of MOR during opioid withdrawal may bring this receptor into close proximity with the cannabinoid receptor, promoting direct receptor associations. Unlike most cell-membrane bound GPCRs, the cannabinoid receptor has a predominantly intracellular distribution in the brain (Rozenfeld, 2010). The distribution of CB1r within somatodendritic structures in the LC agreed with this distribution pattern (Scavone et al., 2010). Interestingly, in the LC somatodendritic MOR was observed to shift from its typical plasmalemmal localization to an intracellular distribution in response to naltrexone precipitated opioid withdrawal (Scavone and Van Bockstaele, 2009). If CB1r and MOR have similar subcellular distribution patterns during opioid withdrawal situations, hetero-dimerization may be a distinct possibility. Using cannabinoids to target this heterodimer during opioid withdrawal may then influence not only cannabinoid signaling, but perhaps also restore normalcy to dysregulated opioid pathways.

In addition to the possibility of direct CB1r-MOR associations, cannabinoid-opioid interactions may also occur at the signal transduction level since both receptors signal through the $G_{i/o}$ alpha subunit, targeting the cAMP pathway. During opioid withdrawal, studies have demonstrated increased abundance of $G_{i/o}$ alpha in the coeruleo-cortical pathway during opioid withdrawal (Nestler et al., 1989, Nestler, 1992). If compensatory changes in CB1r signaling transduction occur during opioid withdrawal, this may also account in part for the efficacy of cannabinoids in reducing opioid withdrawal signs observed both in preclinical and clinical studies.

Cannabinoid modulation of endogenous opioid synthesis and release is yet another candidate mechanism that may contribute to WIN-mediated attenuation of opioid withdrawal signs (Figure 2). Cannabinoid agonists have been shown to facilitate endogenous opioid signaling. Acute exposure to cannabinoid agonists increased extracellular levels of endogenous opioids (Pugh et al., 1995, Pugh et al., 1996, Pugh et al., 1997, Houser et al., 2000), and chronic cannabinoid exposure increased the abundance of endogenous opioid precursors such as prodynorphin, proenkephalin and pro-opiomelanocortin (Corchero et al., 1997a, Corchero et al., 1997b, Manzanares et al., 1998). Cannabinoid stimulation of endogenous opioid release has been linked to the attenuation of opioid withdrawal in an animal model. Exposure to Δ^9-THC enhanced enkephalin release in the NAc attenuated the signs of naloxone-precipitated withdrawal (Valverde et al., 2001). Similar approaches could be taken within the coeruleo-cortical pathway to determine whether the WIN interventions used to attenuate withdrawal in morphine-dependent rats also facilitate endogenous opioid release within the LC. Anatomical studies in the LC demonstrated that pre-synaptic CB1r-positive terminals contacted mu-opioid receptor-containing dendrites (Scavone et al., 2010). Presynaptic CB1r may be poised to regulate or facilitate neurotransmitter and neuropeptide release on to LC neuron; enkephalin release may help to stabilize the LC during opioid withdrawal.

c. Implications of cannabinoid-induced alterations in opioid function in the LC

We previously identified important opposing CRF and opioid influences on LC activity and that changes in the sensitivity to one neuromodulator altered sensitivity to the other. Specifically, we showed that chronic opiate administration selectively increased the sensitivity of LC neurons to CRF (Xu et al., 2004). This was apparent as an increased magnitude of activation produced by microinfused CRF, as well as by stress. More importantly, sensitization of LC neurons to CRF in chronic morphine rats translated to a change in the behavioral repertoire in response to a challenge (Xu et al., 2004) Thus, exposure of morphine-dependent rats to swim stress resulted in excessive climbing at times when control rats would adopt a passive coping strategy of immobility. Climbing behavior

in this model has been linked to activation of the brain norepinephrine system (Detke et al., 1995). This represents an example of how the level and mode of LC activity is the result of a balance of neuromodulators that are engaged and active at a particular time. The mechanism by which chronic opioids induce postsynaptic sensitization to CRF in LC neurons is currently unknown, although many changes in intracellular signaling systems within LC neurons have been documented to occur as a result of chronic opiate administration and these could contribute to altered postsynaptic sensitivity to CRF (Nestler et al., 1999).

Along these lines, it is critical to determine how repeated cannabinoid use affects MOR function in the LC. As cannabinoids significantly affect behavioral regulatory processes known to be LC-specific, such as the modulation of attention, arousal, anxiety and stress (Muntoni et al., 2006, Nestler, 1999), cannabinoid-induced alterations in MOR activity within the LC may likely sensitize this region to input from stress-related pathways, and may underlie the behavioral abnormalities and cognitive deficits seen with repeated cannabinoid use. Long-term cannabinoid use is associated with a syndrome of cognitive impairment that notably includes significant attentional dysfunction, and anxiety and stress disorders (Chaperon and Thiebot, 1999, Lundqvist, 2005, Demuth and Molleman, 2006).

V. Potential Therapeutic Targets of Cannabinoid-Opioid Interactions

a. Cannabinoid-induced decreases in opiate withdrawal expression

In the area of therapeutic utility, cannabis can be recommended as a palliative medical alternative for patients with multiple sclerosis and spinal cord problems where it has been shown to alleviate pain, muscle spasms and convulsions. In addition, it can be recommended to cancer and AIDS patients in order to prevent vomiting and nausea, which result as side effects of chemotherapy, radiation therapy and antiretroviral medications. It also stimulates appetite in people who suffer from this medical condition. Similarly, the therapeutic use of marijuana slows chronic pain and helps attenuate the tics in patients with Gilles Tourette's syndrome. It also may be useful both in the reduction of physical and stress-related symptoms, which occur following the cessation of drug abuse. However, cannabis plays no role in curing these conditions, but only acts to ease their symptoms. Even in the abovementioned cases, there exist contraindications, and cannabis use is not recommended for use in patients with psychotic disorders and psychological or heart problems, cardiac arrhythmias, heart failure or patients who have had angina or a heart attack. Currently Dronabinol and Nabilone as cannabinoids are available for clinical use, but there are few studies reporting on their real effectiveness.

Because the cannabinoid system interacts so closely with the opioid system, the cannabinoid receptors are attractive potential therapeutic targets. Despite this, assessment of cannabis for the reduction of opioid withdrawal has been limited to qualitative survey data rating the efficacy of illicit substances for withdrawal symptoms (Hermann et al., 2005). At present, strict regulation of cannabinoid compounds and political controversy prevent rigorous clinical assessment of cannabinoid testing in the clinical setting. However in the absence of controlled clinical studies, data from experimental animal models provide an excellent source of information regarding potential therapeutic cannabinoid regimens. A number of preclinical studies investigating cannabinoid modulation of opioid dependence and withdrawal may have therapeutic implications for the treatment of the opioid withdrawal syndrome in the clinical population. Clinically, withdrawal from heroin or prescription opioids is characterized by a host of quantifiable physical and emotional symptoms that may include muscle aches and pain, agitation and anxiety, nausea, gastrointestinal upset, tachycardia, rhinorrhea, and chills (Wesson and Ling, 2003). Similarly, in animal models of opioid dependence, withdrawal behaviors can be quantitatively assessed to determine whether cannabinoids can mediate the opioid withdrawal syndrome (Gellert and Holtzman,

1978, Fernandez Espejo et al., 1995). The use of various cannabinoid agents designed to augment or block cannabinoid signaling has been tested to determine their effects on the development of opioid dependence and the expression of opioid withdrawal.

By targeting the cannabinoid system and in turn modulating opioid signaling in noradrenergic cells, it may be possible to reduce the severity of opiate withdrawal signs (Figure 3). Numerous studies have demonstrated that endocannabinoid or delta-9-tetrahydrocannabinol (Δ9-THC) exposure during morphine withdrawal in both mice and rats reduces the severity of morphine withdrawal symptoms (Frederickson et al., 1976, Vela et al., 1995, Lichtman et al., 2001, Valverde et al., 2001, Yamaguchi et al., 2001, Del Arco et al., 2002, Cichewicz and Welch, 2003). Several studies have displayed the potential of endocannabinoid interventions for normalizing opioid system dysfunction. Attenuation of morphine-withdrawal has also been achieved via administration of the endogenous cannabinoids 2-arachidonoylglycerol and anandamide (Vela et al., 1995, Yamaguchi et al., 2001). Common withdrawal behaviors diminished due to Δ9-THC administration were jumping, weight loss, head shakes and paw tremor, although findings varied considerably depending upon dosing paradigm (Vela et al., 1995, Lichtman et al., 2001, Yamaguchi et al., 2001). Peripheral effects of naloxone-precipitated withdrawal were also attenuated by Δ^9-THC in guinea pig ileum (Frederickson et al., 1976). Only one study to date has tested the efficacy of a synthetic cannabinoid agonist, and found that HU210 was similarly efficacious to Δ^9-THC and the endocannabinoid 2-arichidonoylglycerol (2-AG) in reducing instances of paw tremor and jumping behavior. Interestingly, administration of Δ^9-THC was shown to attenuate signs of morphine withdrawal through facilitation of endogenous enkephalin release (Valverde et al., 2001), an endogenous opioid that targets the opioid receptors in the LC (Johnson et al., 2002, Barr and Van Bockstaele, 2005). This finding is especially important given that endogenous peptide levels are decreased in response to chronic opioid exposure in LC pathways (Van Bockstaele et al., 2000).

Cannabinoid antagonists may also have therapeutic utility if administered prior to the development of opioid withdrawal. Modulation of opiate withdrawal behavior, associated protein expression, and morphine-sensitivity has also been achieved by administration of cannabinoid receptor antagonist SR141716A in chronic opiate-exposed rodents (Rubino et al., 2000, Lichtman et al., 2001, Navarro et al., 2001, Singh et al., 2004, Vigano et al., 2004). Along similar lines, cannabinoids also appear to modulate heroin seeking behaviors, though there is debate in the literature as to the nature of these effects. Several groups have shown that SR141716A can negate the reinforcing and motivational properties of heroin in animals trained to self administer the drug (Navarro et al., 2001, De Vries et al., 2003, Fattore et al., 2005b). Others provide evidence for Δ^9-THC-mediated enhancement of opioid self-administration (Solinas et al., 2004, Ellgren et al., 2007), which may also support a role for cannabinoid antagonists in the prevention of heroin-seeking. Collectively, these findings support the presence of functional crosstalk between cannabinoid and opioid systems and the ability to demonstrate this phenomenon using a variety of models and addiction paradigms.

b. Insights into Potential Cannabinoid-Opioid Therapeutic Targets from the Clinic

The debate surrounding medicinal cannabinoids has received added attention recently as regulatory concerns may prevent full consideration of studies that report multiple clinical applications for cannabinoids (Cohen, 2009a, b, 2010). Applications for medicinal cannabinoids that are already under investigation include the treatment of nausea, anorexia, neurodegeneration, inflammation, excito-toxicity and pain. The appetitive and anti-emetic properties of cannabinoids have led to the approval of their use in chemotherapy and AIDS patients. There is growing evidence for therapeutic cannabinoid effects on inflammatory and excito-toxic cellular processes that are linked to epilepsy, Parkinson's disease, amyotrophic

lateral sclerosis, spasticity, and CNS injury (Robson, 2001, Ramirez et al., 2005, Steffens et al., 2005, Machado Rocha et al., 2008, Garcia-Arencibia et al., 2009, Onaivi, 2009, Bosier et al., 2010, Fernandez-Ruiz et al., 2010, Gowran et al., 2010). Increasing numbers of publications have reported on the critical role of the cannabinoid system in addiction and substance abuse (Fattore et al., 2007a, 2008, Bosier et al., 2010), as well as the potential for potent modulation of the opioid system by cannabinoids (Fattore et al., 2005a, Lopez-Moreno et al., 2010, Robledo, 2010, Tucci, 2010).

Despite increasing accumulations of preclinical data suggesting that cannabinoid benefits may outweigh the risks in certain serious medical conditions, political conflict over the legalization of medicinal marijuana continues to preclude a smooth transition of these preclinical studies into clinical trial testing. This may persist in the near future as state and federal government debates over cannabis regulations continue. However, there are many therapeutic alternatives to smoking or ingested cannabis. The development of compounds designed to modulate endocannabinoid levels or the use of synthetic cannabinoids with well-defined pharmacological properties may address many of the concerns associated with legalization of medical marijuana. In the meanwhile, indirect approaches can be taken to assess cannabinoid modulation of the opioid system among individuals in treatment for substance abuse. Co-abuse of cannabis and opioids is quite common in substance abusers, and investigation of this polydrug use may provide clues as to how cannabinoid-opioid interactions play out in the substance abuse treatment setting.

c. Concurrent Cannabis and Opioid Use

Cannabis use is particularly widespread among opioid-dependent individuals (Nurco et al., 1988, Nirenberg, 1996), and numerous studies have examined the concurrent use of cannabis and opioids. Within those seeking treatment for opioid dependence, cannabis is consistently reported to be among the most frequently co-abused substances, along with benzodiazepines and cocaine. Estimates of cannabis use in clients have ranged anywhere from 20% to 95% of the population (Saxon et al., 1990, Nirenberg, 1996, Budney et al., 1998, Church et al., 2001, Epstein and Preston, 2003, Nixon, 2003, Aharonovich et al., 2005). The prevalence of cannabis use varies by geographical location, likely due to the associated changes in drug availability, cost, and potency. Nonetheless, despite this variability, cannabis use remains a prominent characteristic of the drug use profile of many opioid users. Among those prescribed chronic opioid therapy for pain, cannabis use was significantly more common than in the general population in every age group (Reisfield et al., 2009). Based on these observations, co-abuse of cannabis and opioids has become the focus of many clinical research initiatives.

The prevalence of cannabis use has been established within a number of methadone maintenance programs by urinary drug screen (UDS). For example, Marammani observed within a cohort of 1090 heroin-dependent individuals presenting for methadone maintenance between 1994 and 2005, that 64.6% of men and 57.1% of females reported concurrent opioid and cannabis use when entering treatment (Maremmani et al., 2010). One study of 98 males on MMT found that 55.1% used cannabis during treatment (Saxon, 1993), while another study reported an even higher 79% rate of use (Nirenberg, 1996). Cannabis use was evaluated prior to and during treatment in a sample of 196 persons in an Israeli methadone maintenance program. At treatment intake, 25% reported current cannabis use, and 52% had at least one cannabis-positive UDS during the first year of treatment. Approximately one-third of the sample met the cannabis abuse criteria, and used cannabis for at least three consecutive months during treatment (Weizman et al., 2004). In a study designed to determine predictors of relapse in 74 heroin-dependent individuals, 47.3% of the methadone-maintained sample reported using cannabis during the 8-week study period (Wasserman et al., 1998). Finally, in a retrospective analysis of cannabis use from three

clinical trial cohorts on methadone maintenance (n=408), 30.6% of the individuals in care were categorized as occasional users (≤1/6 UDS cannabis positive), while 23.3% demonstrated frequent use (>1/6 UDS positive) (Epstein and Preston, 2003).

Cannabis use has also been examined among individuals participating in other opioid-dependence treatment modalities. As part of a buprenorphine and behavioral therapy treatment trial, Budney, et al. reported that 66% of their sample of opioid dependent patients tested positive for cannabis use at least once during the 26–32 week study period; users of cannabis had an average of 45% of UDS result in cannabis-positive findings (Budney et al., 1998). Among 47 individuals on a 6-month outpatient naltrexone therapy program, cannabis use was also prevalent, observed in at least once in 68% of the sample with an average of 47% of all UDS's being cannabis-positive (Church et al., 2001). Raby (2009) observed only 38.1% of 63 opiate dependent individuals were cannabis abstinent during outpatient naltrexone treatment, while 28.6% were intermittent cannabis users, and 33.3% were classified as consistent cannabis users (Raby et al., 2009).

Longitudinal studies over the course of treatment have also revealed interesting trends. While some have observed levels of cannabis use to remain stable or increase early in treatment (Raby et al., 2009), other have failed to demonstrate this effect (Gottheil et al., 1993, Weinstein et al., 1993). In a study comparing the rates of cannabis use at months one, six, and twelve of maintenance treatment, there were differences between methadone and heroin maintenance. Among those on methadone maintenance, rates of cannabis-positive UDS fall from 63% at the start of treatment to 57.1% six months later, finally dropping to 48.5% at the one-year mark. Meanwhile those on heroin maintenance increase over the study period from 54.5% to 69.5% (Musshoff et al., 2009).

d. Cannabis Use During Treatment for Opioid Dependence

Investigations of the effects of cannabis in opioid-dependent individuals have often focused upon the impact of cannabis use on treatment for opioid dependence. Among the outcomes assessed were treatment retention, illicit drug use, medication compliance, relapse, risk behaviors and opioid withdrawal signs. However, to date the findings remain equivocal as the as to the impact of cannabis use on outcomes of medication assisted treatment. Additionally, numerous studies provide neutral evidence that cannabis use does not appear to significantly alter the course of treatment for opioid addiction.

Other illicit drug use rates do not appear to increase during treatment for opioid dependence among those using cannabis. There were no significant correlations between cannabis use and the likelihood of testing positive for opioid, benzodiazepine or cocaine use in a group of buprenorphine-treated persons (Budney et al., 1998), or in methadone-maintained individuals (Saxon, 1993, Epstein and Preston, 2003, Scavone et al., 2013). Findings from a meta-analysis on predictors of substance use in treatment-seeking opioid dependent individuals found evidence for concurrent cannabis and opioid use during treatment, but no prospective effects of cannabis on increased opioid use following completion of treatment (Brewer et al., 1998). Several studies have demonstrated that retention in treatment for opioid dependence was unaffected by the use of cannabis either prior to or during treatment (Saxon, 1993, Budney et al., 1998, Epstein and Preston, 2003, Weizman et al., 2004). However the long-term nature of MMT often renders retention a poor indicator of overall treatment outcome. Among MMT patients, chronic cannabis use also did not alter control of heroin craving and withdrawal signs (Nava et al., 2007). Additionally, no increases in psychological distress, infectious disease, and risk-taking behavior were observed within a cohort of methadone-maintained individuals testing positive for cannabis use (Weizman et al., 2004). Cognitive function and employment were not found to be significantly different between cannabis-users and cannabis-abstinent individuals undergoing MMT (Saxon, 1993).

Moreover, regardless of cannabis use, disruptions in normal hypothalamic-pituitary-adrenal (HPA) axis function due to opioid abuse were restored to normal following methadone maintenance treatment (Nava et al., 2007).

We recently examined the question of cannabis use in a longitudinal fashion ina sample of individuals seeking outpatient medication assisted treatment. Retrospective chart analysis was used and examined past and present cannabis use and its association with opiate abstinence, dose stabilization, and indices of treatment compliance. Consistent with the literature, objective rates of cannabis use were high during methadone induction, dropping significantly following dose stabilization. History of cannabis use correlated with cannabis use during MMT, but did not appear to negatively impact the methadone induction process. Pilot data also suggested that objective ratings of opiate withdrawal decreased in MMT patients using cannabis during stabilization. The present findings may point to novel interventions to be employed during treatment for opiate dependence that specifically target cannabinoid-opioid system interactions (Scavone et al., 2013).

While much of the existing research finds a lack of evidence for harmful cannabis effects on treatment for opioid-dependence, several studies have revealed detrimental associations across diverse populations. Cannabis use was associated with more rapid lapse to heroin use within a cohort enrolled in MMT (Wasserman et al., 1998). While no impact of cannabis use on treatment outcome was noted within an outpatient buprenorphine treatment trial coupled with behavioral therapy, cannabis use was associated with drug dealing and needle sharing factors (Budney et al., 1998). Interestingly, following inpatient treatment for substance abuse, post-discharge cannabis use was associated with faster relapse to alcohol and cocaine use, but was unrelated to heroin use (Aharonovich et al., 2005). However, among individuals receiving chronic opioid therapy for pain, the presence of cannabis use was a positive predictor of future opioid misuse (Reisfield et al., 2009). Within the general population, cannabis use was also strongly associated with increased risk for other substance use and dependence (Degenhardt et al., 2001).

Interestingly, several studies have demonstrated that under certain circumstances, cannabis use can be associated with positive treatment prognosis among opioid-dependent cohorts. For example, Epstein and Preston (2003) found that cannabis abuse and dependence were predictive of decreased heroin and cocaine use during treatment. Intermittent use of cannabis (defined as ≥1 but ≤ 99% positive drug screens) was associated with a lower percentage of positive opioid UDS and improved medication compliance on naltrexone therapy (Church et al., 2001). Similarly, associations of intermittent or occasional cannabis use with improved retention in treatment for opioid dependence have also been reported (Ellner, 1977, Raby et al., 2009). Among opioid-dependent individuals undergoing naltrexone therapy, intermittent cannabis users (with 1–80% of UDS positive for cannabis) fared better than cannabis abstinent or consistent cannabis users in terms of treatment retention and medication compliance (Raby et al., 2009 010 #715, Lopez-Moreno et al., 2010, Robledo, 2010).

An important consideration is the response to cannabinoid therapies in the substance-dependent population, which may differ significantly from drug naïve or recreational substance users. Within adolescents, frequent cannabis use doubles the risk for depression and anxiety, and significantly decreases multiple indices of psychosocial functioning (Brook et al., 1999, Brook et al., 2002, Patton et al., 2002). Indisputably, chronic cannabis exposure in large doses has negative psychological and health consequences (Hollister, 1986, Kendler and Prescott, 1998, Budney and Moore, 2002, Patton et al., 2002, Lundqvist, 2005, Rubino and Parolaro, 2008). However, obvious differences would be expected in the responses to cannabinoid exposure in the opioid dependent population given the many physiological adaptations that occur with long-term drug exposure and typical psychiatric co-morbidity.

The risks associated with cannabis use in the opioid-dependent population must be weighed against the prospective benefit of successful substance abuse treatment outcomes and the prevention of the much greater risk and harm association with opioid addiction.

VI. Conclusions

Opioid dependence and withdrawal are complex biological processes that appear to be subject to the influence of cannabinoids. The findings from basic and pre-clinical studies in rodent models highlight several potential mechanisms through which cannabinoids may modulate the phenomenon of opioid withdrawal, and call attention to the importance of cannabinoid-opioid interactions within noradrenergic brain circuits such as the coeruleo-cortical pathway. Preclinical studies that continue to explore the safest and most effective means of using cannabinoids to target disrupted noradrenergic circuits will be central to the progress within this field of research. Like many pharmacological therapeutics, the use of cannabinoids does not come without risk and will continue to require assessment of the impact of its use to treat conditions such as opioid withdrawal in humans. Determining whether cannabinoids have therapeutic efficacy in clinical populations similar to that reported in animal models will be extremely important. Ultimately, the knowledge gained from the preclinical and clinical research studies described within this review highlights important and exciting new avenues for future research that continue to investigate cannabinoid effects on noradrenergic circuit dysfunction during opioid dependence and withdrawal. Future studies may contribute to the development of novel cannabinoid-based therapeutics that provide clinicians an additional tool to support the recovery of opioid-dependent persons undergoing treatment.

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Highlights 3–5 bullet points (maximum of 85 characters, including spaces, per highlight) to describe only core results of the paper

Review of the problem of opioid dependence and withdrawal

Review of cannabinoid effects on noradrenergic circuitry

Review of cannabinoid opioid cross-talk

Targeting cannabinoid opioid interactions in novel therapeutic approaches

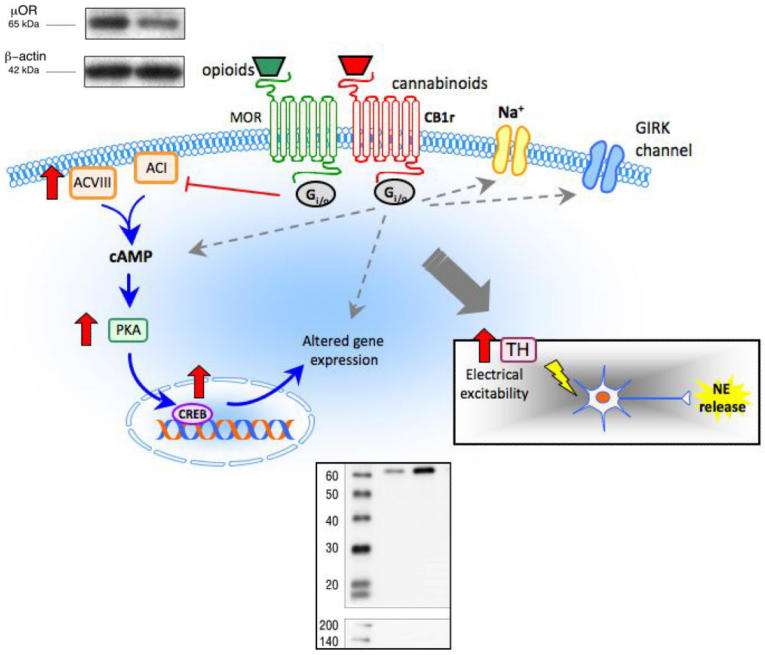

Figure 1.

Schematic illustration depicting putative interactions between the cannabinoid and opioid systems in LC neurons (see text for details). Using a combination of behavioral, biochemical and neurochemical approaches, chronic cannabinoid administration has been shown to increase multiple indices of noradrenergic activity, including increases in tyrosine hydroxylase (TH) expression in the LC (Western blot, bottom right). In contrast, chronic administration of a CB1r agonist decreases MOR expression in the LC (Western blot, top left). Opioid and cannabinoid receptors mediate common signaling pathways central to clinical issues of tolerance, dependence and addiction. The interaction of these receptor systems is supported by findings of cross-tolerance, mutual potentiation, and receptor cross-talk. Downstream effectors of CB1r modulation could lead to altered neuronal excitability and to alterations in opioid receptor signaling that are central to the etiology of anxiety, stress–related dysfunction and the management of pain.

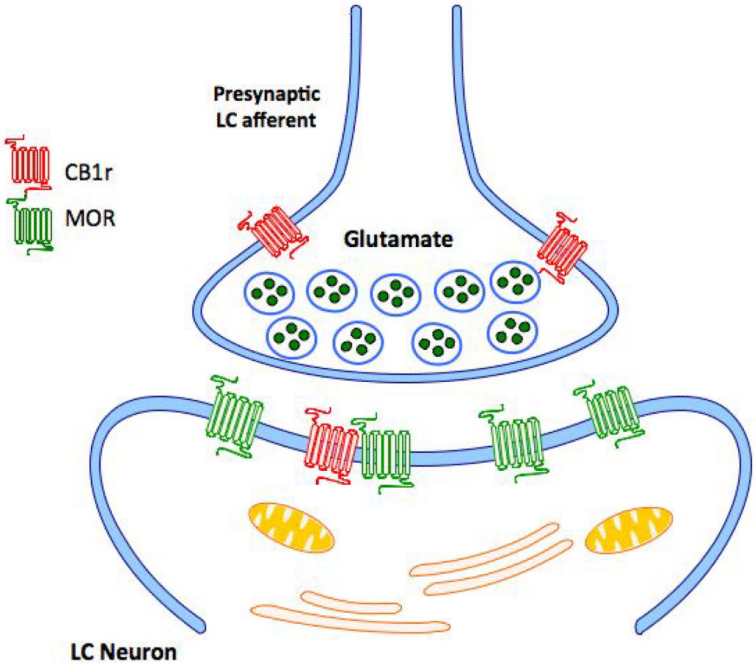

Figure 2.

Sites of action for CB1r modulation of noradrenergic circuitry include noradrenergic and GABAergic axon terminals in the frontal cortex, noradrenergic cell bodies in the LC as well as CB1r modulation of afferent input to the LC. Modulation of CB1r localized to presynaptic axon terminals in the LC, many of which are of the excitatory-type, may contribute to an attenuation of glutamatergic drive, a well-characterized hallmark of opiate withdrawal.

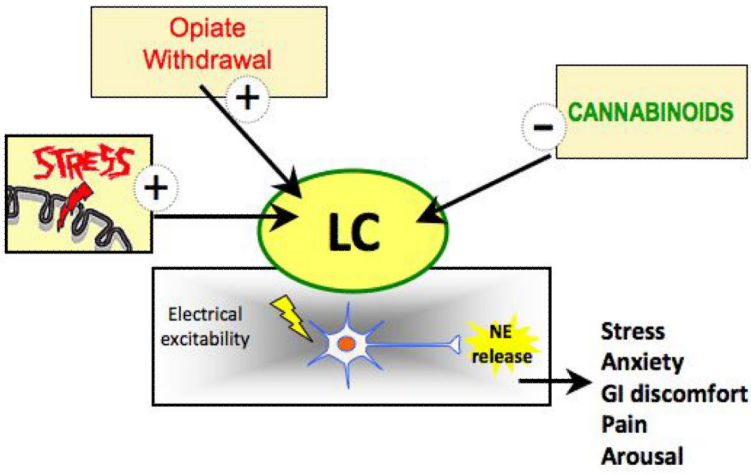

Figure 3.

Emerging knowledge of how the LC-norepinephrine system is regulated by stressors and determinants of sensitivity of LC neurons to prolonged opioid exposure is an important step in understanding and alleviating stress-induced relapse to drug abuse. Engagement of the endocannabinoid system in modulation of noradrenergic neurons could lead to altered neuronal excitability that improve behavioral dysfunction observed in anxiety, stress–related dysfunction and opiate dependence and withdrawal.