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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 comorbid mental disorders. Research over the past decade has shed light on the influence of endocannabinoids (ECs) on the opioid system. Evidence from both animal and clinical studies point toward an interaction between these two systems, and suggest that targeting the EC 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 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 the management of opiate dependence and withdrawal.

Key words: norepinephrine, locus coeruleus, endocannabinoid, stress, marijuana, clinical.

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Background

Overall, illicit drug abuse in the United States exceeded $180 billion in 2008 according to the 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 States approximately $8.6 billion, and this number continues to rise (Birnbaum et al., 2006; Gilson and Kreis, 2009; Strassels, 2009).

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Abbreviations: 2-AG, 2-arachidonoylglycerol; AC, adenylyl cyclase; CB1r, cannabinoid type 1 receptors; CREB, cAMP response element binding protein; CRF, corticotropin releasing factor; EC, endocannabinoid; HPA, hypothalamic–pituitary–adrenal; LC, locus coeruleus; MMT, methadone maintenance treatment; MOR, mu-opioid receptor; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; PGi, paragigantocellularis; PKA, protein kinase-A; UDS, urinary drug screen.

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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.

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 one 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 by 170% and 450% respectively from 1994 to 2002. Furthermore, opioid-related deaths rose by more than 300% between 1999 and 2006 (OAS, 2009).

THE CLINICAL OPIOID WITHDRAWAL SYNDROME AND UNDERLYING BRAIN CIRCUITRY

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 similar 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