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Historical Review: Opiate Addiction and Opioid Receptors

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Abstract

Substance use disorders (SUDs), defined as a collection of symptoms including tolerance and withdrawal, are chronic illnesses characterized by relapse and remission. In the United States, billions of dollars have been lost due to SUDs. In the past 30 years, effective medications and behavioral interventions have played a major role in preventing relapse and facilitating longer periods of abstinence. From the late 1990s to the present, the opioid epidemic or opioid crisis in the United States has raised public awareness of SUDs. Methadone, buprenorphine, and naloxone have proven their effectiveness in treating addicted individuals, and each of them has different effects on different opioid receptors. Methadone and buprenorphine target mu opioid receptors (MORs) in the brain to treat opioid dependence by reducing withdrawal and craving, whereas naloxone is an opioid antagonist used to treat opioid overdose. Mu, kappa, and delta are opioid receptor subtypes with common analgesic effects, and each also has unique effects and distribution in the brain. MORs in distinct brain regions, such as the nucleus accumbens and basolateral amygdala, trigger the euphoria and incentive properties of rewarding stimuli. Kappa opioid receptors can trigger anti-reward effects and produce dysphoric effects. Delta opioid receptors can induce anxiolytic effects. Though effective medications are available, relapse is still common due to neurobiological changes in brain pathways and tolerance of opioid receptors with repeated abuse of substances. In this article, I summarize the biological mechanisms of opioid dependence and opioid receptors and review previous articles about medications used to treat SUDs and their clinical effects.

Keywords

substance use disorders, opioid addiction, opioid receptors, methadone, buprenorphine, naloxone

Introduction

Substance use disorders (SUDs) are chronic illnesses characterized by relapse and remission[1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), SUDs are defined as a collection of symptoms, including tolerance development, withdrawal, uncontrolled increasing intake, and craving for a substance[2]. In the United States, 17% of the population use tobacco products, 25% of adults consume binge-levels of alcohol, and 7% are diagnosed with alcohol use disorders[3,4]. Though illicit drug use of heroin, cocaine, and amphetamine is less common, it is more highly related to medical illness and to increased costs of health care and the criminal justice system. In the United States, billions of dollars have been lost due to prescription opioid abuse annually. Despite the significant stigma, both in society and the medical community, effective medications have been developed in the past 30 years. The treatment of SUDs with medication and behavioral interventions can play a major role in preventing relapse and facilitating longer periods of abstinence[5,6].

From the late 1990s to the present, the opioid epidemic or opioid crisis in the United States has raised public awareness of SUDs and the number of medications used to treat opioid dependence has increased[7]. Methadone, a full mu opioid agonist, and buprenorphine, a partial mu opioid agonist, are used to treat people with opioid dependence by reducing withdrawal and craving symptoms[8,9]. Indeed, methadone maintenance therapy (MMT) can help intravenous drug users reduce human immunodeficiency virus (HIV) transmission, by reducing their frequency of injection. Naloxone is a specific

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opioid antagonist that targets mu, kappa, and delta opioid receptors to treat opioid overdose[10]. Though current medications have proven to have positive effects on opioid intoxication and reducing withdrawal and craving symptoms, relapse and remission are still common among opioid users. Risk of relapse is heightened due to the increase in tolerance of opioid receptors and neurobiological changes in brain pathways caused by repeated abuse of opioids.

In this article, we summarize the biological mechanisms of opioid dependence and opioid receptors. We also review previous articles about the medications used to treat opioid dependence, focusing on their clinical effects on different opioid receptors.

Biological Mechanisms of Opioid Dependence

At the onset, most people use opioids to have euphoric feelings or to control pain. However, tolerance develops easily and leads to increased uncontrolled intake; combined with a craving to minimize withdrawal symptoms, opioid dependence develops as a consequence. Euphoric feelings easily fade as tolerance develops, but the withdrawal symptoms persist. Patients with severe opioid dependence experience terrible, uncomfortable feelings such as muscle ache, bone pain, tearing, runny nose, yawning, diarrhea, abdominal cramps, agitation, anxiety, and sweating during opioid withdrawal[2,11].

Medications can alleviate withdrawal symptoms to help patients feel more comfortable after stopping opioid use. Reducing withdrawal symptoms and feelings of craving can also help patients remain abstinent, preventing them from using the drug again to relieve withdrawal symptoms—that is to say, stop the vicious cycle of continuous drug dependence.

Medications for the treatment of SUDs can be classified into three groups: full agonists, partial agonists, and antagonists[12]. Methadone, similar to heroin, is a full agonist targeting mu opioid receptors(MORs). The half-life of methadone in an opioid-tolerant patient is approximately 24 h, which is longer than the half-life of heroin. Patients who used methadone as replacements do not experience withdrawal and craving symptoms during that period; by preventing them from experiencing uncomfortable feelings, they are less likely to relapse[13]. Partial agonists such as buprenorphine were developed as an alternative to methadone. Buprenorphine does not stimulate MORs to the same degree as full agonists; thus, patients using buprenorphine, compared with methadone, are less likely to have respiratory depression and euphoria[14]. Naloxone and naltrexone are antagonists that target all opioid receptor subtypes. Antagonists compete with agonist to bind to opioid receptor, but do not stimulate it; thus, they do not cause pharmacological effects such as sedation, analgesia, respiratory depression, and euphoria. Naloxone's affinity is highest for the MOR and is used to prevent respiratory and mental depression in opioid overdose patients. Naltrexone targets both MORs and kappa opioid receptors (KORs); long-term injectable naltrexone is used to decrease heroin use[15].

Opioid Receptors

Opioid receptors are G protein-coupled receptors distributed across the brain, spinal cord, skin, and gastrointestinal tract[16–18]. Opioids and many metabolites can cause sedation, analgesia, euphoria, and respiratory depression by stimulating opioid receptors in the brain. Tolerance and dependence to opioids develop rapidly; thus, withdrawal symptoms such as diarrhea, bone pain, and goosebumps are very common among chronic users[19,20].

Opioid Receptors Subtypes, Distribution, and Physiological Responses

Mu, kappa, and delta are opioid receptor subtypes that share a common analgesic effect on brain circuits; however, each of them has unique effects and specific distribution in regions of the brain[21,22]. MORs, which are locate in cerebral cortex, thalamus, and periaqueductal gray, bind endorphins and stimulate euphoria, physical dependence, and respiratory depression. MORs in distinct brain regions such as the nucleus accumbens and basolateral amygdala trigger euphoria and the incentive properties of rewarding stimuli, playing an important role in goal-directed behavior. As addictive behavior develops, poor decision making and cognition impairment shift the goal directed behaviors to habitual behaviors, and lead to compulsive drug use[23,24]. KORs, which locate in hypothalamus, periaqueductal gray, bind with dynorphins and trigger dysphoric effects and sedation. The delta opioid receptors (DOR), located in basal ganglia, bind with enkephalins and induce anxiolytic effects (Table 1)[20,25].

Opioid Receptors and Psychological Reactions

The MOR was discovered first[26]. Because MOR can trigger euphoria, it is essential for stimulating the reward system[27,28]. Indeed, human neural sensitivity to social rejection and social hedonic capacity is associated with a MOR gene (A118G)[29]. Moreover, recent mice studies suggest that MOR plays a key role in social attachment and anhedonia[30]. As opioid tolerance develops among opioid-dependent patients, increased craving for more opiates at the expense of naturally rewarding stimuli emerges; as a result, reward system homeostasis and social function become compromised[31]. Social dysfunction due to substance use is one of the 11 criteria for SUD in DSM-5, and social anhedonia among addicted individuals is of increasing interest in recent research[2]. The reward system is highly dynamic across the lifetime, and MORs are involved in this system. Recent studies demonstrate that the effect of MOR varies with age, in particular during adolescence[32]. In an adolescent mouse study, social peer exploration behaviors can be substituted

Table 1. Opioid Receptors, Subtypes, CNS Location, Effects, and Specific Effects.

Subtypes	CNS location	Effects	Specific effects
Mu	Cerebral cortex, thalamus, periaqueductal gray, and rostral ventromedial	Analgesia, euphoria, constipation, respiratory depression, physical dependence	Reward reinforcements (hedonic and Incentive)
Kappa	Hypothalamus, and periaqueductal gray	Analgesia, diuresis, dysphoria	Anti-reward
Delta	Basal ganglia(pontine nucleus, amygdala)	Analgesia, anxiolysis	

Table 2. Medication for Opioid Use Disorders.

Domain	Methadone	Buprenorphine	Naloxone	Naltrexone
Mechanism of action	Full mu-receptor opioid agonist	Partial mu-receptor opioid agonist	Opioid antagonist	Opioid antagonist
Typical dosing	80–120 mg/day	8–24 mg/day	Varies	20–150 mg/day
Half life	15–22 h	20–70 h	1–1.5 h	4 h
Side effect	Respiratory depression	Respiratory depression uncommon	Withdrawals in people with opioids in their system	Diarrhea and abdominal cramping
Clinical use	Better retention (approximately 50%)	Low potential of abuse due to coformulation with naloxone	Reversing the respiratory depression caused by opioids	Treating alcoholism or alcohol dependence

by morphine-triggered MOR stimuli[33]. Adolescent and adult rodents also have different patterns of heroin self-administration and seeking[34]. Increased positive reinforcement of MOR and fewer opioid withdrawal symptoms in adolescent animals is consistent with the notion that adolescents are more likely to initiate addictive behaviors than adults[35].

The KORs can trigger anti-reward effects, thereby producing dysphoria[36]. In an adolescent rat study, KOR was associated with a decrease in social play[37]. Social or physical stressors, such as prolonged exposure to drugs of abuse can enhance KOR function through corticotropin-releasing factor (CRF) signaling, thus promoting relapse among addicted individuals[38,39]. In addition, stress due to long-term drug exposure can produce a depressant effect. Indeed, KOR antagonists may be used to treat depressive disorder, in particular among addicted individuals[40]. A recent study suggests that a KOR antagonist had no effect on naïve rats without previous alcoholism, but reduced craving behaviors in rats with previous alcohol dependence[41]. In conclusion, KOR has anti-reward effects throughout the process of addiction and has the opposite effect of MOR. While addiction develops, the intensified stress can enhance the function of KOR, contributing to dysphoric mood during both withdrawal and abstinence states, leading to relapse.

The activation of DOR can reduce levels of anxiety and attenuate depressive symptoms[42]. Previous studies demonstrate that DOR may play a role in alcohol consumption, but its exact role in the abuse of other drugs is still unclear[43,44].

Medication Treatment

As mentioned above, addicted individuals develop dependence and tolerance; thus, withdrawal symptoms are inevitable. Among chronic users, one reason for the continued use of a substance is to stave off withdrawal symptoms. Heroin and morphine have a relatively short half-life: 2–3 min and 2–3 h, respectively[45,46]. Withdrawal symptoms such as sweating, abdominal pain, diarrhea, and craving for drugs follow a few hours later. Opioid agonist therapy can reduce the intensity of euphoria and withdrawal and has a longer half-life, so it can stabilize the lives of chronic users, leading to housing and employment opportunities. Compared with full agonists, partial agonists have a smaller effect on respiratory depression and can be combined with antagonist to effectively treat chronic abuse (Table 2).

Methadone, a full MOR agonist, triggers a similar opioid receptor effect, but has a different pharmacokinetic profile. It has some agonist action at KOR, and is also a possible DOR and weak N-methyl-D-aspartate (NMDA) antagonist[47]. In the brain, stimulation of MOR can cause euphoria, analgesia, constipation, and respiratory depression. Because methadone has a longer half-life (approximately 15–22 h) and fewer drug-like effects, such as euphoria, it causes fewer withdrawal symptoms and is less reinforcing[48]. Indeed, MMT can decrease the intensity of craving, such that patients are no longer preoccupied with drug-seeking behaviors. Thus, patients are more willing to remain in treatment, and mental health care providers can continue working with patients to improve their psychosocial function in areas of employment and family and social relations[49–51]. The most dangerous risk associated with methadone use is respiratory depression; in particular when using in combination with sedative-hypnotics and/or alcohol[52]. Previous studies indicate that MMT can reduce criminal activity and change the route of drug administration from intravenous to oral among drug users, reducing HIV transmission from contaminated needles[53,54]. Typical methadone doses are in the range of 80–120 mg/day and addicted individuals must report to a clinic for observed daily dosing at the beginning of MMT[55].

Buprenorphine is a partial agonist with high affinity for MOR. It is also a partial KOR agonist or functional antagonist (possibly with antidepressant effects), and a weak DOR antagonist. Buprenorphine has a half-life of approximately 20–70 h[56,57]. Doses start between 4 and 8 mg sublingually once a day and maintenance doses range from 8 to 24 mg daily. Compared with the full MOR agonist, buprenorphine has a ceiling effect when it binds to and activates MOR; specifically, buprenorphine provides less euphoric feelings, as well as respiratory depression, making it safer than methadone, but adequate for relieving opioid withdrawal even in highly tolerant patients[58]. Buprenorphine in combination with naloxone, a competitive opioid receptor antagonist, is used commonly to treat opioid use disorder in the United States. Buprenorphine monotherapy is reserved for pregnant women, who have a higher risk for adverse effects if exposed to naloxone. Due to its high affinity, buprenorphine can displace full agonists from MOR and precipitate mild-to-moderate withdrawal when treatment is initiated. If a patient has crushed and injected an oral form of buprenorphine with naloxone, which cannot be absorbed orally, both buprenorphine and naloxone can precipitate severe opioid withdrawal[59]. Evidence supports positive outcomes for patients treated with buprenorphine, as well as MMT. However, meta-analysis of multiple comparative trials have found that patients on MMT are more likely to remain in treatment, compared with patients on buprenorphine treatment[50,51].

Nalbuphine is a MOR antagonist and a KOR agonist, and is indicated for the treatment of moderate-to-severe pain. Among addicted individuals, nalbuphine may precipitate withdrawal symptoms[60].

Naloxone and naltrexone are both opioid antagonists, and naloxone has a higher affinity than naltrexone. Naloxone is a non-selective and competitive opioid receptor antagonist, and is used for acute opioid overdose, reversing respiratory and mental depression caused by opioids[61]. As mentioned above, naloxone can be combined with buprenorphine to decrease the risk of injection misuse. Naltrexone is used primarily to treat alcoholism or alcohol dependence. Long-acting injectable naltrexone can decrease the craving and the risk of overdose, by blocking opioid receptors. However, data on effectivity are limited in the United States. Treatment for addicted individuals should be preceded by successful detoxification because naltrexone may cause withdrawal symptoms, leading to low adherence[62,63].

Conclusion

In 2007, in the United States, $55.7 billion (USD in 2009) were lost due to prescription opioid abuse. Workplace, health care, and criminal justice costs accounted for $26 billion, $25 billion, and $5 billion, respectively[64]. In 2013, 127,000 deaths were caused by SUDs, with one of the highest number of deaths (51,000) caused by opioid use disorder[65]. The peak developmental period for the highest prevalence of SUDs is late adolescence and early adulthood, age range from 18 to 25 years[66].

Opioid dependence among this particular age group may change the course of a lifetime; drug seeking and craving can ruin an individual's education and employment opportunities, and can even lead to criminal activity resulting in incarceration. As mentioned above, animal studies provide evidence that adolescents are more likely to initiate addictive behaviors because they have more positive feedback from MOR and less opioid withdrawal symptoms compared with older age groups.

Opioid agonist and/or antagonist medication are proven to be effective treatments for opioid dependence, with specific effects for each type of medication. Opioid agonist therapy can reduce the intensity of euphoria and withdrawal, and opioid antagonist therapy can prevent the misuse of opioid replacement medications. Methadone—a full MOR agonist—is the best choice for retaining patients in treatment programs. Buprenorphine—a partial agonist—is a safer alternative to methadone due to less respiratory depression. Naltrexone is used in combination with buprenorphine. Long-acting injectable naltrexone can decrease cravings, but has limited adherence. Methadone stimulates a greater MOR response in the brain compared with buprenorphine.

As mentioned above, opioid receptors are associated with reward processing. Though the associations between patient adherence to treatment programs and MOR stimulation are still not clear, medications with a greater effect on MOR, in particular the response to rewarding stimuli are more likely to increase patient adherence because the effects would decrease gradually instead of sharply.

The ultimate aim of opioid dependence treatment is to stabilize the patients' medical, psychiatric, legal, family, housing, and employment problems; modifying their associations to rewarding stimuli from substances to daily life events may be the fastest way to change their behavior patterns.

Changing the sensitivity of opioid receptors may play an important role in modifying reward processing among those receiving opioid agonist/antagonist treatment, in particular young addicted individuals and those who quit drugs completely. Investigating changes in sensitivity of opioid receptors may provide useful information to evaluate the severity of opioid dependence. In addition, it may provide a useful tool for evaluating the effectiveness of current medications when patients are in treatment programs. Further research on the associations between changes in sensitivity of opioid receptors and opioid dependence is needed.

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