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Novel Treatment Strategies for Cocaine and Opioid Abuse

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Introduction

The abuse of drugs is a serious universal problem. Drug addiction is considered to be a chronic, relapsing disorder characterized by an uncontrollable drug craving regardless of serious health problems [1,2]. Repeated drug use arises due to the positive reinforcing effects produced by drugs that lead to neurological changes in the brain's reward circuits [1,3]. Drug addiction has also been reported to involve another source of reinforcement such as, withdrawal symptoms. Positive (e.g., euphoria) and negative (e.g., withdrawal symptoms) reinforcement together provide a strong motivational force for obsessive drug intake leading to addiction [2]. The neurological changes and behavioral abnormalities that are associated with drug addiction may persevere for months or years after termination of drug use. The characteristic behaviors of addiction include tolerance, sensitization, dependence, withdrawal and craving [1].

Cocaine is one of the oldest and most powerful psychoactive substances. It is widely abused and perhaps the most reinforcing of all drugs of abuse [4,5]. Cocaine was used in early 1900s to treat chronic pain, asthma, wasting diseases, and nervous exhaustion and was also used as a local anesthetic during surgical procedures [6]. Globally, cocaine use is considered to be concentrated in Western Europe and the Americas, but it is thought to be spreading quickly geographically. In the latest World Drug Report, the United Nations Office on Drugs and Crime (UNODC) reported that cocaine consumption has increased in Europe and some West African countries over the past decade [7]. After a single dose, the effects begin immediately and disappear within a few minutes or hour. When consumed in small amounts, cocaine typically causes the user to feel euphoric, energetic and mentally alert [8]. The duration of these effects depends upon the route of administration. The powerful central nervous system (CNS) stimulation caused by cocaine is followed by depression [4,6,9]. However, the exact physiology related to depression after using cocaine is unknown, but it has been linked to catecholamine or other neurotransmitter depletion. The short-term physiological effects of cocaine use include: constricted blood vessels, dilated pupils, and increased heart rate, blood pressure, and body temperature. Some users experience restlessness, irritability, anxiety, and paranoia. Severe medical complications are also associated with cocaine use including cardiovascular effects (cardiac arrhythmia and heart attacks), neurological effects (strokes, seizures, headaches, and coma) and gastrointestinal complications (abdominal pain and nausea). In rare cases, sudden death can occur on the first use of cocaine or unexpectedly thereafter. This is often a result of cardiac arrest or seizures followed by respiratory arrest [5,7,10]. The risk of cocaine adverse effects increases with increasing doses or frequency of administration. Additionally, due to the use of cocaine in shooting galleries and sharing of injection equipment, cocaine addiction has been associated with increased risk of HIV, hepatitis B and C and violence [10,11]. The disastrous health and social consequences of cocaine abuse made the development of an effective treatment a high priority.

The medicinal value of opium has been agreed on for centuries. In spite of having an extensive side-effect profile, morphine, isolated from opium, remains the gold standard for treating chronic or persistent pain. Activation of the μ-opioid receptors located in the regions of brain and spinal cord that transmit pain are responsible for the majority of the physiological and behavioral effects of morphine [12-14] Morphine is a lipophilic compound and is available as sulphate, atartrate and hydrochloride salt. Morphine has been considered the drug of choice for treating moderate to severe pain. Its short half-life allows frequent changes in dosing according to the individual needs. The low cost of morphine solution and immediate-release formulations and its potential availability are the major reasons for it to be recommended as a first-line opioid in the WHO Cancer Pain Relief Guidelines [15]. However, its narrow therapeutic index and severe side effects limit its therapeutic use. The most prominent side effects are respiratory depression, decreased gastrointestinal motility and the development of dependence, withdrawal symptoms after chronic administration [16-18]. In therapeutic doses morphine also causes euphoria, sedation, nausea and vomiting [14]. One of the major side effects of morphine administration is development of tolerance to the analgesic effect [13]. Adaptation process can be one of the underlying causes of tolerance to opioids. The sources for adaptation can be traced back to the cellular and molecular level. Opioids show selective tolerance i.e. tolerances to different opioid effects develop at different rates. While tolerance to nausea, vomiting, sedation, euphoria and respiratory depression occur immediately, the tolerance to constipation and miosis is minimal. This diversity suggests receptor-related differences in the rate of development of tolerance to opioids.

Sigma Receptor Ligands

Sigma receptors have gained much attention in recent years with their involvement in various neurological disorders, drug addiction and cancer. Initially sigma receptors were identified as a subtype of opioid receptors. Based on behavioral studies of morphine-like drugs in dogs, Martin et al. [19] named this distinct class of receptor as 'sigma'. Subsequent studies clearly demonstrated that sigma receptors are a unique class of binding proteins with a distinct ligand selectivity pattern and specific anatomical distributions from other proteins [20-22].

Numerous drugs of different classes have a high binding affinity to sigma receptors, these include psychotomimetic benzomorphans, cocaine and its derivatives, amphetamine, some neuroleptics, atypical

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antipsychotic agents, anticonvulsants, monoamine oxidase inhibitors, histaminergic receptor ligands, and several steroids [23-26]. These compounds led to the pharmacological identification of sigma receptors as unique receptors differentiating them from opioid receptors. The autoradiographic localization of sigma receptor binding sites was accomplished using a range of radioligands, such as [^{18}F]FTC-146, [^{3}H](+)-SKF-10,047, [^{3}H](+)-3-PPP, [3-(3-Hydroxyphenyl)-N-(1-propyl) piperidine], [^{3}H]haloperidol, [^{3}H]DTG, [^{3}H](+)-pentazocine [22,27-31].

To date, two subtypes of sigma receptors have been identified, sigma-1 and sigma-2, based on their respective size, distribution in various tissues and affinity for enantiomers of benzomorphans [32,33]. Both sigma-1 and sigma-2 receptors are thought to be involved in the anti-cocaine activity. However, only the involvement of the sigma-1 receptors is well documented [28]. Several studies have shown that cocaine preferentially exert its psychostimulant effect by binding to sigma-1 receptors. It is believed that, sigma-1 receptors influence the actions of cocaine through three different mechanisms, 1) direct binding to the receptors, 2) modulation of other neurotransmitter systems, and 3) alterations in gene expression [34,35]. Matsumoto et al. confirmed that low doses of novel sigma receptor antagonists could notably inhibit convulsions and lethality induced by toxic doses of cocaine. In addition, the cocaine toxicity was augmented by sigma-1 receptor agonists, indicating the likely involvement of sigma-1 receptors in cocaine-induced toxicity [30,36]. Hence, developing synthetic small molecule antagonists for sigma-1 receptors will be an effective strategy in the development of potential therapeutic candidate for cocaine abuse.

Mitragyna Speciosa

Mitragyna speciosa Korth is a tropical plant indigenous to Southeast Asia. The leaves of the plant have traditionally been used by natives as a substitute for opium or to treat withdrawal, as well as for their stimulant effects [38-40]. Furthermore, the leaves have also been used by southern Thai villagers as a medicine to treat coughing, diarrhea, muscle pain and hypertension. Mitragynine and 7-hydroxymitragyne, corynanthine-like alkaloids, have been reported to be responsible for the opioid properties found in this plant [38,41]. Though, the structures of mitragynine (66% of the alkaloid content) and 7-hydroxymitragynine were different from morphine, in pharmacological studies these compounds showed agonistic effects on opioid receptors [42]. Having a novel structural scaffold for opioid receptor affinity and activity, mitragynine and 7-hydroxymitragynine promote further investigation as novel lead compounds for the development of therapeutics for opioid abuse.

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