Chapter 1

Cocaine: Usage, Misuse, and Addiction Processes. An Overview

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Abbreviations

5HT 5-hydroxytryptamine; serotonin
ACTH Adrenocorticotropic factor
CPP Conditioned place preference
CPu Caudate putamen
CRF Corticotropin releasing factor
D1/D2 Dopamine receptor 1/2
DA Dopamine
DAT Dopamine transporter
Enk Enkephalin
HPA axis Hypothalamic–pituitary–adrenal axis
KOPR κ-Opioid receptor
MOPR μ-Opioid receptor
NAc Nucleus accumbens
NE Norepinephrine
NET Norepinephrine transporter
Pdyn Prodynorphin
SERT Serotonin reuptake transporter
VTA Ventral tegmental area

INTRODUCTION

Cocaine is one of the most widely abused illegal drugs in the world and addiction to cocaine is a devastating public health problem with major medical, economic, and social costs. The 2013 National Survey of Drug Use and Health has reported that at least 1.5 million people are estimated to be active cocaine users in the United States, and a separate survey reported that there are at least 15 million users worldwide (Degenhardt & Hall, 2012). Derived from the *Erythroxylum coca* plant, cocaine has been used since ancient times and its excitotoxic effects having been characterized during the late nineteenth century in Western Europe and North America. However, as its highly addictive and aberrant behavioral effects (such as psychosis in some cases and extreme paranoia in others) were elucidated, it became classified as an illicit substance. Cocaine usage began to spike during the 1970s and 1980s with the highest abuse rates peaking during the 1990s. Nevertheless, over 1.5 million people are estimated to be active cocaine users in the United States alone and the drug has a

CLINICAL PERSPECTIVES ON COCAINE ABUSE

Historical Cocaine Use

Cocaine is purified natural product derived from the *E. coca* plant, used in unrefined form since pre-Columbian times, initially chewed by the native peoples of Bolivia and surrounding areas to enhance concentration, similar to our use of caffeine today. Despite its excitotoxic effects having been characterized during the late nineteenth century in Western Europe and North America, its psychostimulant properties were used in numerous medicinal tonics during the early twentieth century (for example, famously in Coca Cola). However, as its highly addictive and aberrant behavioral effects (such as psychosis in some cases and extreme paranoia in others) were elucidated, it became classified as an illicit substance. Cocaine usage began to spike during the 1970s and 1980s with the highest abuse rates peaking during the 1990s. Nevertheless, over 1.5 million people are estimated to be active cocaine users in the United States alone and the drug has a
devastating impact on a wide range of aspects of human society including, but not limited to, personal and public health, economics, private and public domestic life, and national/international criminal justice and public policy issues. It should be noted that, unlike opioid drugs, violent crime is often associated with cocaine use, due to the aggressive behavior and bravado/arrogance cocaine has been reported to induce in users.

Clinical Features of Cocaine Addiction

Unlike opioid drugs, it is estimated that only 10–15% of individuals that try cocaine will progress to heavy use (abuse) and ultimately to addiction. There appears to be both environmental (for example, stress) and genetic (for example, in the PDYN gene) correlates to individual susceptibility to cocaine addiction (further discussed below) (Levran et al., 2014). Like most drugs of abuse, cocaine follows a cycle of addiction consisting of initial use, progression from intermittent to regular use concomitant with escalation of dosage (preaddiction), addiction concomitant with measurable neurobiological changes and persistence of these changes, withdrawal, a modest period of abstinence, depressive symptoms, and relapse. However, unlike opioid drugs, cocaine addiction may develop more slowly (Gawin, 1991). It should also be noted that similar with other drugs of abuse, human immunodeficiency virus is comorbid with cocaine usage, especially among Hispanics and African Americans (Novick et al., 1989).

A human cocaine addict tends to consume vast quantities of the drug in a single drug-taking session usually lasting 4–24 h and occurring as often as 1–7 days a week (cocaine “binges”). These “binges” are characterized by a surge in accumulation of the neurotransmitter DA in the synapse due to the block of reuptake (Maisonneuve, Ho, & Kreek, 1995; Maisonneuve & Kreek, 1994). However, cocaine has additional effects beyond block of DA reuptake and perturbs many neurotransmitter systems (serotonin and norepinephrine (NE) reuptake are also inhibited). Nevertheless, the DA surge is typically followed by an abstinence phase (“crash”) characterized by a depressed mood (dysphoria), loss of pleasure (anhedonia), and extreme lethargy, concurrent with reductions in DA (Gawin & Kleber, 1986; Zhang et al., 2013). Interestingly, significant physical dependence, as determined by measurable physiological changes, does not occur in cocaine addicts but instead an intense psychological craving and dependence, which ultimately leads an individual to recurring “binge/crash/abstinence” cycles. Because of the lack of significant physical withdrawal symptoms, for many years it was thought that cocaine had a minimal or only an acute effect on brain function (Gawin, 1991). However, thanks to an extensive body of research, we now know the alterations in brain molecular biology and neurochemistry induced by cocaine that induce craving ultimately persist even beyond successful intervention and disruption of the “binge” cycles (Henry & White, 1991; Zeigler, Lipton, Toga, & Ellison, 1991).

Indeed, one of the most significant and unique aspects of cocaine addiction is the high rate of recidivism among abstinent cocaine users, even in the absence of psychological/physiological withdrawal symptoms or drug cravings. The frequency of relapse—even after years of abstinence—has been reported to be as high as 70% and can be instigated by numerous phenomena which we have put in descending, approximate rank order: (1) the drug itself, (2) stressors of all kinds, and (3) cues/situations associated with previous drug use (Bossert, Ghitza, Lu, Epstein, & Shaham, 2005). Unlike opiates, cocaine does not have a single target that is able to account for all of its effects and numerous hypotheses have been generated in order to elucidate mechanisms involved in relapse-like behavior such as changes in glutamate transmission, the dynorphin/KOPR system (see below) and more recently, the endocannabinoid pathway, the latter two may represent viable targets for potential pharmacotherapies in the treatment of this devastating and prevalent disease. Of particular significance is the role of stress in inducing relapse to cocaine-seeking, as cocaine use is known to induce plastic changes to the responsiveness of the body’s primary stress responsive system, the HPA axis, and these alterations will be discussed elsewhere. However, stress-induced relapse is hallmark of virtually all drugs of abuse as are drug-associated cue-induced reinstatement (such as presentation with a specific situation, location, or object previously experienced during drug taking) (Gawin, 1991).

Genetic and Environmental Factors Contributing to Individual Susceptibility to Cocaine Dependence: Endogenous Opioid System and Stress

Interestingly, only 10–15% of individuals who try cocaine will become addicted highlighting the importance of genetic and environmental influences, especially stress, to the development of cocaine addiction. Based on rigorous twin studies, it has been estimated that genetics may account for 30–60%, and as high as 78%, of the risk of susceptibility to cocaine addiction (Kendler, Jacobson, Prescott, & Neale, 2003; Kreek, Nielsen, Butelman, & LaForge, 2005). In rodent behavioral models, different strains of inbred and outbred rats and mice respond to cocaine differently, and since these animals are bred and raised in highly controlled laboratory conditions, this argues for the significance of genetics in susceptibility to cocaine addiction (Mantsch, Ho, Schlussman, & Kreek, 2001; Schlussman, Ho, Zhou, Curtis, & Kreek, 1998; Zhang, Schlussman, Ho, & Kreek, 2001). Due to cocaine’s well-established effects on DAergic neurotransmission, analysis of genes involved in DA synthesis, degradation, and release has been considered and several gene variants have been identified that correlate with individual variability in responses to cocaine (for example, cocaine-induced paranoia) but few variants have been identified that have been definitively linked to addiction (Haile, Kosten, & Kosten, 2007). However, in a study by our group, Levran et al. (2014) report that numerous polymorphisms in multiple components of the DAergic system are correlated to cocaine addiction in African Americans, and several of these genetic variants overlap with genetic susceptibility of heroin addiction as well.

The endogenous opioid system is also involved in regulating DAergic transmission of the mesolimbic reward pathway and adaptation in opioid genes may underlie cocaine dependence (Kreek et al., 2012). Indeed, work by our laboratory and others has shown in rodent models that chronic cocaine administration upregulates expression of µ-opioid receptor (MOPR; encoded by OPRM1), but no changes in its endogenous ligand β-endorphin or the related ligand enkephalin (Enk) have been identified, thus leading to a relative dynorphin deficiency. However, an upregulation in expression of KOPR and its endogenous ligand dynorphin
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(encoded by PDYN) occurs concurrent with sensitization in intracellular signaling pathways downstream of KOPR (Daunais, Roberts, & McGinty, 1993; Forman & Estilow, 1988; Moldow & Fischman, 1987; Piras, Zhou, Schlussman, Ho, & Kreek, 2010; Spangler, Unterwald, & Kreek, 1993; Unterwald, Horne-King, & Kreek, 1992; Unterwald, Rubenfeld, & Kreek, 1994). Taken together, this state of relative endorphin deficiency coupled with dynorphin/KOPR excess lead to feelings of dysphoria during abstinence and subsequent exacerbation of drug craving and facilitation of relapse. Polymorphisms in opioid genes may confer either resilience or susceptibility to dependence, depending on the functional consequences of the different variants. In fact, polymorphisms in OPRM1, PDYN, and OPRK1 (the genes that encode the MOPR, dynorphin, and KOPR, respectively) have all been correlated to the susceptibility to develop cocaine dependence (Dahl et al., 2005; Kreek et al., 2012, 2005; Williams et al., 2007; Yuferov, Levran, Proudnikov, Nielsen, & Kreek, 2010). This work and its functional significance have been extensively reviewed by our laboratory and others and will therefore not be discussed further here. However, mutations in opioid genes are insufficient to account for the relatively low rate of dependence among cocaine users. Genetic variability does not exist in a vacuum; it is most likely the synergistic combination of environmental factors acting on genetic variants that predispose an individual to becoming a cocaine addict. Of course, one cannot become a cocaine addict unless one is exposed to cocaine and given the opportunity to try it in the first place, and this initial exposure is a poignant sociological issue but beyond the scope of this chapter. However, one study of interest found that rats isolated during adolescence self-administered more cocaine as adults, which suggests a role for specific social situations during childhood as a possible factor contributing to susceptibility of cocaine addiction (Baarendse, Limpens, & Vanderschuren, 2014).

Stress is a ubiquitous environmental factor affecting numerous biological processes and the role of stress in addiction is well established and has been discussed in detail by our group and others (Koob et al., 2014; Mantsch et al., 2014; Picetti et al., 2013). In brief, stressors activate the HPA axis, which consists of the secretion of corticotropin releasing factor (CRF) from the ventromedial hypothalamus, which acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH), which ultimately acts on the adrenal cortex to secrete cortisol (corticosterone in rodents).

Acute cocaine use results in a rapid increase in circulating ACTH and cortisol (corticosterone) both in human and in rodent models (Baumann et al., 1995; Moldow & Fischman, 1987), an effect that may be dependent on DA (Borowsky & Kuhn, 1991), but levels of hormones and messenger (m)RNA expression of HPA axis components return to baseline levels after a few days post cocaine administration (Zhou et al., 1999). Chronic cocaine usage modulates mRNA expression of various components of the HPA axis, including CRF and CRF receptors in the hypothalamus, amygdala, and nucleus accumbens (NAc) (Koob, 2010; Zhou et al., 1996), and general HPA axis responsiveness (Zhou, Proudnikov, Yuferov, & Kreek, 2010). CRF also has central actions as well and its receptors are widely expressed in numerous brain regions including limbic structures. It is a well-characterized phenomenon in rodent behavioral models that various types of stressors potentiate addictive-like behaviors in the conditioned place preference (CPP; greater time spent in conditioned chamber with stressful stimuli administered prior to drug compared with drug alone) and self-administration (stress induces greater self-administration) paradigms. CRF1 antagonists that are injected directly into the rodent brain are able to attenuate cocaine self-administration under extended-access conditions, which suggests that the central effects of CRF1 play a significant role in cocaine addiction (Specio et al., 2008). Furthermore, it has been reported both in clinical studies and in rodent behavioral models that stress often precedes cocaine taking and enhances cocaine reward (Sinha, 2009). Stress also contributes to greater cocaine self-administration under extended-access conditions (Mantsch et al., 2001). Taken together, these data suggest a bidirectional feedback between cocaine and stress can promote and exacerbate cocaine dependence.

Interestingly, stress is known to induce dynorphin release and activate the KOPR, facilitating feelings of dysphoria (Land et al., 2008; McLaughlin, Marton-Popovic, & Chavkin, 2003). Therefore, it has been suggested that stress-induced KOPR activation may facilitate cocaine seeking by depressing mood (Butelman, Yuferov, & Kreek, 2012). Indeed, studies by our group and others have also shown that stress can induce epigenetic changes in the PDYN gene that result in increased dynorphin mRNA expression (Reed et al., 2012). The studies presented in this section taken together suggest that the synergistic relationship between environmental stress and mutations in the dynorphin/KOPR system may act to promote cocaine dependence in susceptible individuals but additional research is needed to elucidate the precise mechanism.

MOLECULAR NEUROBIOLOGY OF COCAINE ADDICTION

Historical Research on the Mechanism of Action of Cocaine

Seminal studies conducted in the 1970s and 1980s revealed cocaine use resulted in disrupted reuptake of monoamine neurotransmitters such as serotonin (5-hydroxytryptamine, 5HT), NE, and especially DA, thus resulting in their accumulation in the extracellular spaces of the brain, and that the potency of this inhibition directly correlated to self-administration behavior (Heikila, Orlansky, & Cohen, 1975; Ritz, Lamb, Goldberg, & Kuhar, 1987). It was not until the early 1990s that one of the main targets of cocaine, the DAT, was cloned and the occupancy and subsequent inhibition of DAT was shown to be one of the primary mechanisms of cocaine action (Shimada et al., 1991; Volkow et al., 1997) (Figure 1). However, DAT knockout mice still self-administer cocaine which suggests that DA alone is insufficient to account for the rewarding properties of cocaine (Rocha et al., 1998). Indeed, block of reuptake of serotonin and NE are also important actions of cocaine. Interestingly, knockout of the serotonin reuptake transporter (SERT) and the norepinephrine transporter (NET) individually is also insufficient to disrupt cocaine self-administration, suggesting that DA, 5HT, and NE may act in concert to induce the behavioral and rewarding properties of cocaine (Sora et al., 1998).

Nevertheless, pioneering studies even prior to the cloning of DAT, conducted in rodent models, were able to identify key brain regions, now known as the mesolimbic DAergic pathway, as primary sites mediating the rewarding properties of cocaine. Specifically, disruption of either the DAergic neurons of the ventral tegmental area (VTA) or the (NAc, the primary projection site of
FIGURE 1 Cocaine mechanism of action at DA neurons. DA is synthesized in presynaptic DAergic neurons of the VTA through a multienzymatic process that begins by converting tyrosine (Tyr) to L-DOPA via the action of TH. Upon excitation of DA neurons, DA is released into the synapse where it acts on postsynaptic DA Receptors (D1–D3), where it modulates adenyl cyclase activity. DA is cleared from the synapse by reuptake through the DAT. Cocaine acts by binding to the DAT and preventing DA reuptake, thus leading to an accumulation of DA in the synapse and subsequent overstimulation of postsynaptic DA neurons. Adapted from Maisonneuve and Kreek (1994).

Development of Humanized Behavioral Models of Cocaine Addiction

Oddly, it was believed for many years that cocaine use had no long-term impact on brain neurophysiology, primarily due to the lack of significant physical withdrawal symptoms, and most research employed behavioral models primarily using only acute cocaine administration. Yet, self-administration, a classical behavioral model to test the abusive properties of drugs developed in the early 1960s (Weeks, 1962), had been used to show that given unlimited access to cocaine, rodents and nonhuman primates self-administer large quantities of cocaine. Nevertheless, most rodent behavioral models utilized acute and/or low-dosage, short-access nonhumanized models that did not accurately recapitulate human cocaine usage in many respects. Human cocaine addicts frequently engage in short-term “binges” lasting 4–24 h and occurring anywhere from 1 to 7 days a week followed by abstinence periods and gradual escalation in dose and frequency of “binges” (Gawin, 1991). Unlike the human disease, most rodent models consisted of single, daily injections of a sustained dose or short-duration, low-dose cocaine self-administration paradigms. As such, many groups reported variable molecular findings due to the inconsistencies in the models.

For example, levels of DA receptor D2 were considered in the CPu and NAc by autoradiography binding experiments. Kleven et al. used an investigator-administered single, low dose (10 mg/kg) for 8 days and found transient increases in D2 in the CPu and the NAc while Goeders et al. administered a single, higher dose (15 mg/kg) for 15 days and found decreased D2 in the CPu and increased D3 in the NAc (Goeders & Kuhar, 1987; Kleven, Perry, Woolverton, & Seiden, 1990). Which group’s behavioral experiment was most relevant to the human disease and revealed accurate information about cocaine-induced changes in D2 expression?

As an attempt to resolve the temporal and dosage issues, our laboratory pioneered the development of the “binge” model, which consists of three consecutive injections (one every hour) per day for either 1–3 days for acute exposure or 14 days, which may utilize escalating dosages (higher “binges”), for chronic exposure models (Branch, Unterdorf, & Kreek, 1992; Maisonneuve et al., 1995; Spangler et al., 1993; Unterwald, Cox, Kreek, Cote, & Izenwasser, 1993; Unterwald et al., 1992). Furthermore, injections are only given during the morning (light-on time for rodents), which is the analogous to the period in the circadian rhythm and the time of day (i.e., early evening) when a human addict typically uses cocaine (Gawin, 1991). Referring to the D2 example above, from our laboratory, Unterwald et al. used a 14-day “binge” model with three daily injections of moderate dose (15 mg/kg) and analyzed D2 levels after autoradiography at 2, 7, and 14 days of injections and found transient increases in D2 levels in CPu and NAc by day 7, which had returned to normal by day 14 (Unterdorf, Ho, et al., 1994). Therefore, these findings are most consistent with findings from Kleven et al. Variations on the “binge” model have been employed successfully by other groups to clarify similarly conflicting studies. For example, expression of tyrosine hydroxylase (TH), a critical enzyme in DA synthesis, was examined in the VTA, a primary site of DA synthesis, in various animal models. Trulson et al. using a single dose and single daily injections found no change in TH expression (Trulson, Bab, Joe, & Raese, 1986) while Masserano et al., using twice daily injection (a “binge”-like model) found
Upregulation in TH expression (Masserano, Baker, Natsukari, & Wyatt, 1996). The latter finding has been confirmed by many additional studies, thus validating the rationale for the “binge” model in considering gene expression changes (Nestler, 2004; Vrana, Vrana, Koves, Smith, & Dworkin, 1993).

Cocaine-Induced Neurobiological Adaptations and Gene Expression Changes

Repeated use of a drug of abuse results in compensatory neurobiological changes that potentiate continued use of the drug. Changes in gene expression represent one impact of drugs of abuse on the function of neurons at the molecular level. Employing the “binge” model, our group and others have discovered many molecular changes that may underlie cocaine dependence and the high tendency of addicts to relapse. As mentioned above, the plasticity in the endogenous opioid system may mediate DAergic effects of cocaine. Indeed, we have identified an upregulation in MOPR using quantitative autoradiography in the CPu, NAc, and basolateral amygdala as well as increased circulating β-endorphin, while no changes in Enk mRNA expression were detected, another important endogenous opioid ligand (Branch et al., 1992; Unterwald et al., 1992; Unterwald, Rubenfeld, et al., 1994). A reduction in agonist-stimulated MOPR-dependent adenyl cyclase activity was also reported (Unterwald et al., 1993). Taken together, these data suggest cocaine stimulates MOPR signaling in the NAc and CPu, but chronic stimulation may eventually result in desensitization.

A consistent finding using several different behavioral paradigms is an elevation of dynorphin mRNA and peptide, which acts on KOPR receptors to inhibit DA release from VTA neurons. KOPR is a G-protein coupled receptor that is primarily coupled to the inhibitory G-protein, Gqi, which suppresses adenyl cyclase activity and subsequent reductions in intracellular cyclic adenosine monophosphate (Bruchas & Chavkin, 2010; Tejeda, Shippenberg, & Henriksson, 2012). Indeed, we have shown that the endogenous dynorphin peptide (dynorphin Aβ1-17) is able to stimulate a KOPR-dependent suppression of adenyl cyclase activity (Claye, Unterwald, Ho, & Kreek, 1996). Sensitization of the dynorphin/KOPR system is believed to be responsible for the dysphoria and anhedonia that occurs during cocaine withdrawal as a result of an over-compensatory homeostatic suppression of basal DA that develops through repeated cocaine usage—this is known as the allostatic model of drug addiction (Koob & Le Moal, 2008). Using in vivo microdialysis, we were the first to show directly that dynorphin Aβ1-17 infused directly into the CPu of cocaine-administered mice attenuates cocaine CPP, and locomotor sensitization. Furthermore, we found a dose-dependent reduction in basal and cocaine-induced DA levels (Zhang, Butelman, Schlussman, Ho, & Kreek, 2004). Molecular pharmacology work from our laboratory confirms that in addition to dynorphin release, KOPR intracellular signaling in the VTA is sensitized with chronic cocaine. Taken together, these data suggest an acute cocaine dose results in a surge of DA release from the VTA to act on the CPu and NAc, which in turn synthesize and secrete dynorphin, which is released from neurons projecting from the CPu and NAc onto the VTA to activate KOPR, inhibit cyclase activity, and suppress DA release. As a result of chronic cocaine use, KOPR activity is sensitized so that in the absence of cocaine, DA release from VTA neurons is attenuated below basal levels thus contributing to the feelings of dysphoria and anhedonia that result in recidivism of cocaine use (Butelman et al., 2012; Koob & Le Moal, 2008).

However, many other valid hypotheses and molecular changes exist separate from or in concert with the dynorphin/KOPR allostatic model. For example, chronic cocaine use would be expected to regulate a number of genes in numerous different neuronal populations. The transcription factors AFosB and CREB have both been shown to be acutely upregulated in response to cocaine usage (Robison & Nestler, 2011). CREB has also been shown to directly initiate transcription of dynorphin (Carlezon et al., 1998). The full panel of cocaine-regulated genes, the cell type-specific expression of such genes, and their contribution to cocaine-induced behaviors is continuing to be revealed.

CONCLUSIONS

Although opiate abuse is on the rise, cocaine remains a significant global problem that has staggering social, economic, and medical consequences. Unlike virtually every other known drug of abuse, no Food and Drug Administration-approved, effective pharmacotherapeutic strategies exist. Due to the complexities of cocaine addiction, different treatments have been considered, and may be required, for intervention at different stages in the addiction cycle, primarily: (1) prevention of cocaine use, (2) amelioration of cocaine dependence, and (3) prevention of relapse. As discussed at length above, the dynorphin/KOPR system has important roles in numerous stages of the addiction cycle. Indeed, KOPR agonists blunt/prevent the DA surge thus decreasing cocaine reward in rodent behavioral models (Bidlack, 2014; Butelman et al., 2012). However, high potency KOPR agonists have both dysphoric and hallucinogenic properties in humans. KOPR antagonists may represent potential therapy for relapse prevention and have been shown to successfully block stress and drug-induced relapse-like behavior in rodent models (Butelman et al., 2012). Since both agonist and antagonist properties are desired from a pharmaceutical agent targeting the KOPR, a partial agonist (which can act as either depending on the status of KOPR activation regarding the stage of addiction) would be the ideal agent for treating cocaine addiction. However, this ideal drug targeting the KOPR has yet to be discovered but represents one of the most promising therapeutic targets (Bidlack, 2014). Although much has been learned about cocaine in the past few decades, a great deal is still unknown about cocaine action and the development of addiction. Additional studies may reveal new targets that will one day yield a successful treatment for cocaine addiction and/or prevention of relapse.

APPLICATIONS TO OTHER DRUGS OF ABUSE

Cocaine, like all drugs of abuse, affects DA levels in the mesolimbic reward pathway. However, cocaine is far more complicated since it does not directly affect DAergic transmission but also affects 5HT and NE, thus making its molecular neurobiology significantly more complex. Nevertheless, much of the knowledge learned in behavioral models may be applicable to other drugs of abuse. For example, drug-induced alteration in the HPA axis and KOPR/
Dynorphin system is common to many drugs of abuse. In addition to cocaine, the KOPR/dynorphin system has been heavily studied in alcoholism and many studies report potential therapeutic benefit in modulation of this system in the treatment of alcoholism. Thus, the KOPR/dynorphin system may be a viable therapeutic target for multiple drugs of abuse in addition to cocaine.

DEFINITION OF TERMS

Cocaine It is a psychostimulant drug derived from the *E. coca* plant that acts by blocking reuptake of DA, NE, and 5HT and is widely abused worldwide.

Cocaine “binge” The most common pattern of cocaine use in humans consists of an extended drug-taking session usually lasting 4–24h and occurring as often as 1–7 days a week, followed by a period of abstinence, and then a repeat of the cycle (relapse).

KOPR/dynorphin system It is an endogenous opioid peptidergic system that acts to inhibit DA release from the VTA which is dysregulated in cocaine (and other drug) addiction, which may contribute to the persistence of drug craving and may facilitate relapse behavior.

HPA axis It is the body’s primary stress response that is dysregulated by cocaine (and other drugs of abuse). A wealth of evidence suggests that HPA axis dysregulation (and stressors in general) facilitates development of addiction and promotes relapse behavior.

Genetic susceptibility This describes genetic variants within a population that may perturb some aspect of brain neurobiology that results in an increased likelihood of developing addiction.

Humanized behavioral model of addiction It is a rodent (mouse or rat) experimental behavioral model (usually self-administration or conditioned place preference) that mimics features of human addicts, such as dosage, frequency, and time of use.

Self-administration An operant behavioral model in which the rodent controls the amount of drug that it consumes through activation of a responsive level (or a nose poke) that result in intravenous delivery of drug (numerous variations exist).

Conditioned place preference It is a behavioral model employing an investigator-administered drug that is based on Pavlovian conditioning in which drug is paired with a neutral feature of the chamber (numerous variations on this general paradigm exist) thus establishing an association with the chamber and the reward of the drug.

KEY FACTS OF THE STATISTICS OF COCAINE USE IN THE UNITED STATES

- According to the 2013 National Survey of Drug Use and Health, cocaine is the second most widely abused illegal drug of abuse (after cannabis) in the United States.
- An estimated 1.5 million people are active cocaine users in the United States.
- Adults aged 18–25 years have a higher rate of current cocaine use than any other age group, with 1.1% of young adults reporting past-month cocaine use.
- Overall, men report higher rates of current cocaine use than women.
- According to the 2013 Monitoring the Future Survey, cocaine use among 8th, 10th, and 12th grades has remained steady since 2005 and is at historical lows with about 2.6% reporting past-month use.

SUMMARY POINTS

- Cocaine is a widely used drug that has significant economic, medical, and social costs and is not effective pharmacotherapeutic treatments.
- Cocaine addiction progresses from initial use to repetitive cycles of heavy, short-term use (“binge” use), abstinence, and relapse.
- Unlike other drugs of abuse (which only primarily affect DA release), cocaine’s mechanism of action consists of blocking the reuptake of all monoamine neurotransmitters (DA, 5HT, and NE) by antagonizing the monoamine transporters (DAT, SERT, and NET) thus leading to an accumulation of these neurotransmitters in the synapse of the mesolimbic reward pathway and other regions of the brain.
- Genetic and environmental factors contribute to the susceptibility of an individual to becoming addicted to cocaine, and based on twin studies, it has been estimated that genetics may account for 30–60%, and as high as 78% of this susceptibility.
- Acute cocaine use activates the HPA axis while chronic cocaine use sensitizes the HPA axis and blunts the stress response, which contributes to relapse behavior.
- Accurate behavioral models used to study cocaine addiction, such as self-administration and the “binge” model, are useful because they attempt to recapitulate the human disease.
- Cocaine use results in upregulation of dynorphin mRNA and protein and subsequent elevation of KOPR/dynorphin tone in the VTA/CPu/NAc circuit in virtually every behavioral model tested.
- Modulation of the KOPR/dynorphin system may represent a viable pharmacotherapeutic target for treatment of cocaine addiction.

REFERENCES


