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Review

Sex differences in the neurobiology of drug addiction

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ABSTRACT

Epidemiological data demonstrate that while women report lower rates of drug use than men, the number of current drug users and abusers who are women continues to increase. In addition women progress through the phases of addiction differently than men; women transition from casual drug use to addiction faster, are more reactive to stimuli that trigger relapse, and have higher rates of relapse then men. Sex differences in physiological and psychological responses to drugs of abuse are well documented and it is well established that estrogen effects on dopamine (DA) systems are largely responsible for these sex differences. However, the downstream mechanisms that result from interactions between estrogen and the effects of drugs of abuse on the DA system are just beginning to be explored. Here we review the basic neurocircuitry which underlies reward and addiction; highlighting the neuroadaptive changes that occur in the mesolimbic dopamine reward and anti-reward/stress pathways. We propose that sex differences in addiction are due to sex differences in the neural systems which mediate positive and negative reinforcement and that these differences are modulated by ovarian hormones. This forms a neurobehavioral basis for the search for the molecular and cellular underpinnings that uniquely guide motivational behaviors and make women more vulnerable to developing and sustaining addiction than men.

Contents

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Introduction

Addiction is a chronic, potentially relapsing, neurological illness characterized by a loss of control over drug seeking and intake. Addictive substances include illicit drugs like cocaine and heroin, as well as legally available nicotine and alcohol. Moreover, prescription drugs, such as opioids, stimulants, and depressants are also increasingly being used for non-medical reasons (Compton and Volkow, 2006). Chronic repeated use of these drugs hijacks normal motivated behaviors via the dysregulation of brain reward circuitry (Hyman et al., 2006). While contributions of the neural substrates underlying addiction are being characterized with increasing precision, the overwhelming majority of investigations into brain reward and anti-reward circuitry has been – and continues to be – conducted in men and/or male animals. Until the early 1990s research on the etiology and treatment of addiction was conducted on a male only population because prior to this time the notion that men and women differed only in their reproductive abilities and secondary sex characteristics was embedded in clinical research. Over the past few decades, awareness of the importance of sex differences in addiction has grown and, as a result, an emergent field devoted to characterizing sex differences has and continues to develop (Evans, 2007).

Prevalence

Results of the 2012 National Survey on Drug Use and Health (NSDUH), estimated 9.2% (23.9 million) of Americans, age 12 or older were current (had used in the past 30 days) illicit drug users. While women exhibit lower rates of drug use and addiction than men, prevalence rates indicate that the number of female drug abusers has increased and continues to escalate (SAMHSA, 2012). Evidence identifying important differences in the pattern of drug use and abuse between men and women suggests that gender also influences the course and treatment of substance use disorder. In general, women progress from casual drug use to dependence more rapidly, experience higher levels of craving and relapse during periods of abstinence, take larger amounts of the substance during bouts of relapse, and are less likely to seek treatment for their addiction than men (Brady and Randall, 1999; Ignjatova and Raleva, 2009; Kosten et al., 1985) In addition, women who enter drug abuse treatment programs have a more severe addiction syndrome and higher prevalence of co-occurring mental health disorders (Back et al., 2011; Yates et al., 1993).

Sex differences and influence of ovarian hormone on addiction behaviors

Human studies

The acute subjective effects of most drugs of abuse, except stimulants (cocaine and amphetamine), do not differ between men and women (Terner and de Wit, 2006). In the case of psychostimulants, men often report (but, not reliably) greater subjective effects than women (Lukas et al., 1996). This lack of reliability is likely due to the fact that women's reporting of the subjective effects of their response to psychostimulants varies with the menstrual cycle (Fig. 1). Women have greater subjective responses to cocaine in the follicular phase of the menstrual cycle, when levels of estrogen are rising and progesterone levels are minimal (Evans and Foltin, 2006a; Evans et al., 2002; Sofuoglu et al., 1999). In the luteal phase, when progesterone levels are highest (estrogen levels are also elevated at this time), women report reduced positive subjective effects of cocaine (Evans and Foltin, 2006b; Evans et al., 2002; Sofuoglu et al., 1999). Moreover, administration of progesterone attenuates some of the physiological and positive subjective effects of cocaine (Evans and Foltin, 2006a; Sofuoglu et al., 2004). Taken together, these data indicate that the reinforcing effects of cocaine are strongly influenced by a women's hormonal milieu.

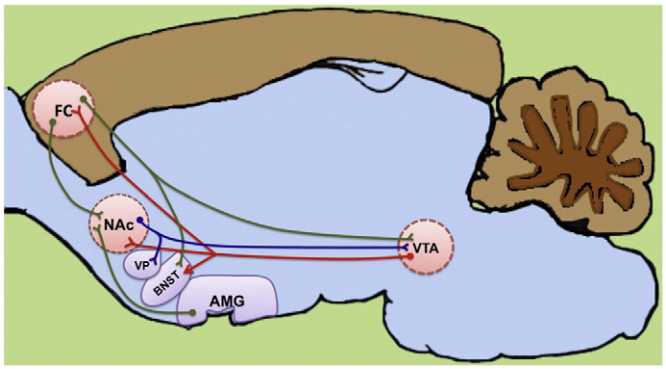

Fig. 1. The human menstrual and rat estrous cycle. The human menstrual cycle (left) occurs over 28 days and is comprised of fluctuating levels of estradiol (E2; top) and progesterone (P4; bottom). Levels of E2 rise to a peak between Days 7 and 14, drop, rise, and then plateau between Days 14 and 28. Progesterone levels rise between Days 0 and 14 from ovulation, reaching their peak at Day 7. The rat estrous cycle (right) is similar but occurs over a 4-day period. Four phases, metestrus, diestrus, proestrus, and estrus comprise the rat estrous cycle. Estrogen levels (top) peak between diestrus (Day 2) and proestrus (Day 1) of the rat estrous cycle, whereas progesterone (bottom) levels reach a peak during the proestrus phase (Day 3).

Animal studies

In preclinical models, the motivational and subjective effects of drugs can be examined using intravenous drug self-administration studies and studies of drug-induced conditioned place preference, respectively (Bardo and Bevins, 2000). Rodent studies have demonstrated sex and hormone related differences in the motivation and subjective effects of drugs of abuse. Specifically, female rats' operant behavior is more robust than males' during acquisition of cocaine and heroin self-administration, escalation of drug intake, and reinstatement of extinguished drug seeking behavior (Lynch and Carroll, 1999; Lynch et al., 2000; Roth and Carroll, 2004). Moreover, female rats acquire intravenous self-administration of cocaine and heroin more quickly and at lower doses than males (Davis et al., 2008; Lynch and Carroll, 1999). In tests of conditioned place preference (CPP), female rats develop CPP at lower cocaine doses than males (Russo et al., 2003b; Zakharova et al., 2009). A recent study from our group was the first to investigate sex differences in drug-primed reinstatement extinguished CPP and found that reinstatement of cocaine CPP is greater for female than male animals (Bobzean et al., 2010). Sex differences in CPP have also been shown for morphine; female rats develop a more robust CPP to lower or much higher morphine doses than males depending upon the strain of rat used in the study (Cicero et al., 2000; Karami and Zarrindast, 2008). These findings reflect the tendency of females to be more responsive to drug-conditioned stimuli than males (Elman et al., 2001; Robbins et al., 1999; Sterling et al., 2004) and may reflect the human condition where women have a higher tendency for relapse into former patterns of drug seeking and taking behaviors.

Ovarian hormones

The observed sex differences in motivational and subjective effects of drugs of abuse are thought to be due to the activational effects of ovarian hormones. This notion is supported by studies assessing the behavioral response to drugs over the course of the estrous cycle. The majority of these studies have been conducted using cocaine as the drug of abuse. Phase of the estrous cycle has been shown to influence an animal's motivation to self-administer cocaine (Roberts et al., 1989) as well as the intensity of cocaine-induced stereotypic and locomotor activities (Quinones-Jenab et al., 1999). Moreover, the psychomotor effects of cocaine and self-administration are higher during estrus compared to other phases of the estrous cycle (Quinones-Jenab