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Addiction and dopamine: sex differences and insights from studies of smoking

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Mesolimbic dopaminergic function influences addiction through effects on reinforcement learning, decision-making, and impulsivity. This review covers sex differences in dopaminergic neurochemistry, their hormonal and genetic determinants, and how differences in dopaminergic tone interact with sex and/or ovarian hormone status to affect cognitive functions. Findings from research on cigarette smoking reveal sex differences in striatal and midbrain dopamine D2-type receptor availability and striatal dopamine release that suggest mechanisms of nicotine dependence, and stronger subjective responses to nicotine and efficacy of nicotine replacement therapies in male smokers than in their female counterparts. Opportunities exist to extend such efforts in studies of how sex and hormone status influence other addictions.

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Introduction: sex differences and dopaminergic signaling in drug use disorders

The prevalence, course, and consequences of substance use disorders differ in men and women. Although men are approximately 70% more likely than women to have a substance use disorder, more women than men (12–49 years of age) recently initiated the use of marijuana, stimulants, heroin, phencyclidine, and alcohol [1]. Women tend to escalate from initiation of drug use to addiction more rapidly than men [2,3], and are more likely than men to relapse after initiating abstinence [4]. Because substance use increases maternal and perinatal morbidity, women experience addiction-related health consequences that do not affect men [5]. They also are disproportionately affected by other untoward effects of drug use, exhibiting a higher relative risk of smoking-related cardiovascular disease [6], and occurrence of cardiovascular [7] and other alcohol-related physical illnesses at lower levels of drinking than men [8].

The National Institutes of Health now has mandated that sex be considered as a biological variable in all biomedical research [9], and sex differences have been evaluated in animal models of addiction and human addiction. This review extends previous syntheses of relevant literature [10,11] on sex differences (and in some cases, similarities) in dopaminergic neurochemistry (for review, see [12]) and addiction. Involvement of dopaminergic systems in the effects of cigarette smoking are highlighted because recent developments and expert recommendations in this research area illustrate an exemplary role for studies of other addictions.

Dopaminergic signaling is central to the etiology and maintenance of substance use disorders by influencing the motivational processes underlying the learning and execution of goal-directed behaviors, as indicated by electrophysiological recordings from midbrain dopamine neurons in monkeys [13,14]. Numerous studies of animal models have implicated striatal dopamine D2-type receptors in vulnerability as well as resilience to addiction [15–22]. These include findings that striatal D2-type receptor availability influences subsequent cocaine self-administration and that striatal D2-type receptors and dopamine transporters show long-lasting neuroadaptations to stimulant administration in nonhuman primates [23,24]. Human studies reinforcing this view show below control striatal dopamine D2-type receptor availability in individuals with addictions to various substances, including stimulants, heroin, alcohol, and tobacco (for reviews, see [25,26]), and (as detailed below) associations of striatal D2-type receptor availability with cognitive functions that affect addiction.

Dopamine signaling, cognition and responses to drugs: effects of ovarian hormones

Cognitive control and adaptive decision-making, functions that are linked to dopaminergic neurochemical markers, influence the course of addictions [27,28]. Impaired cognitive control, measured as impulsivity in personality inventories, has been implicated in the initiation, maintenance, and relapse of drug-seeking behaviors [29]. Stimulant users

are more impulsive than healthy control subjects, and show a negative correlation between impulsivity and striatal D2-type receptor availability (e.g. [30,31]). Conversely, cognitive control, measured in tests of motor response inhibition [32–34] and cognitive flexibility [35,36], show weaknesses in substance abusers, and positive correlations of striatal D2-type receptor availability with performance on relevant tests in healthy controls is disrupted in stimulant users [37,38].

Maladaptive decision-making also is linked to drug addiction and to dopaminergic function. Individuals with substance use disorders of various types discount monetary rewards as a function of their delay more than healthy individuals [39–42]. Stimulant users exhibit correlation between the steepness of the discounting rate and striatal D2-type receptor availability that is not seen in healthy controls [43]. Methamphetamine users also make maladaptive choices and fail to show the relationship between risk and activation in the right dorsolateral prefrontal cortex that is exhibited by healthy control subjects during risk taking in a reward-based laboratory test; instead, they show a linear relationship between riskiness of choice and ventral striatal activation [44]. Moreover, association of response in the dorsolateral prefrontal cortex with riskiness of a decision is highly negatively correlated with striatal D2-type receptor availability in controls [45]. Thus, dopaminergic function, especially signaling through D2-type receptors, can influence addiction by promoting disadvantageous behaviors leading to continued drug use.

Circulating levels of ovarian hormones may influence both striatal dopamine signaling and cognitive control. Estradiol levels are correlated with longer reaction time in motor response inhibition [46] and Stroop task performance [47], suggesting that inhibitory control is weaker when estrogen levels are high. This effect may reflect estrogenic effects on striatal dopamine in that local administration of estrogen into the nucleus accumbens decreases K^+-stimulated dopamine release [48], and estrogen administration to the caudal striatum reduces dopamine D2-type receptor density [49]. Circulating progesterone levels also affect inhibitory control, attenuating impulsive action for sucrose pellets in a Go/No-Go task [50•] and reducing impulsive action for cocaine in a sex-dependent manner [51,52]. Positron emission tomography (PET) imaging in humans has provided only indirect evidence that ovarian hormones may influence striatal DA receptor availability, specifically that D2-type receptor availability was lower in the putamen during the luteal phase of the menstrual cycle, when estradiol and progesterone levels are relatively elevated [53].

Inasmuch as striatal dopaminergic neurotransmission is an important mechanism of subjective response to drugs, associations of hormone status with responses to drugs of abuse also suggest that the hormones influence striatal dopaminergic function. The subjective responses to a number of drugs — most prominently stimulants — differ as a function of hormone levels in women. As reviewed in [23], subjective responses to cocaine tend to be higher during the follicular phase, when hormone levels are low (except for a brief estrogen surge at the end of the follicular phase), compared to the luteal phase, when estrogen and progesterone are elevated. Consistent with that observation, progesterone administration decreases positive subjective effects of cocaine.

Similar investigations in smokers have also revealed effects of ovarian hormones on effects of nicotine and smoking although the direction of the relationship between ovarian hormones and smoking behaviors is less clear. A systematic review and meta-analysis found that higher progesterone levels were associated with both increased negative and decreased positive subjective effects of nicotine. The same review reported higher levels of withdrawal, and a trend toward higher levels of craving, during the luteal (high progesterone) versus the follicular (low progesterone) phase [54]. In oral contraceptive (OC) users, a high dose (0.25 μg) of norgestimate, a synthetic progesterone analog, reduced smoking satisfaction more than a lower dose (0.18 μg), but high levels of endogenous progesterone were positively related to smoking satisfaction in naturally-cycling women [55]. Studies of abstinence-related symptoms in women using a variety of OCs produced mixed findings, with these women reporting less [56] or more [57] craving than those who were not using OCs. Together, these data suggest a likely relationship between ovarian hormones and smoking-related behaviors that may potentially be mediated by hormonal effects on the dopamine system, but a great deal more research is needed to confirm or disconfirm this link and to identify the direction of the relationship. Such investigations may help to clarify the mechanism by which sex differences in dopaminergic signaling and addiction emerge.

Sex differences in the functional genetics of dopamine synthesis and degradation

Sex differences in the physiology of the dopamine system can be traced back to chromosomal differences between men and women. The male-determining gene *Sry*, located on the Y chromosome and found only in (phenotypic) males, is expressed in dopaminergic neurons of the substantia nigra, and influences expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in the biosynthetic pathway to dopamine [58,59]. Estrogen is a regulator of TH activity [60,61], suggesting that different pathways to a similar endpoint are important for regulation of dopaminergic function in males and females.

Catechol-O-methyltransferase (COMT) catalyzes the degradation of dopamine (and other catechols), and a