Sex differences in addiction

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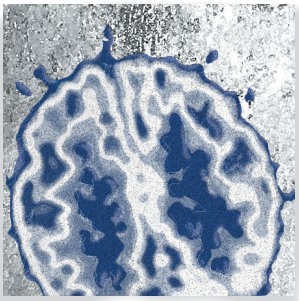

Women exhibit more rapid escalation from casual drug taking to addiction, exhibit a greater withdrawal response with abstinence, and tend to exhibit greater vulnerability than men in terms of treatment outcome. In rodents, short-term estradiol intake in female rats enhances acquisition and escalation of drug taking, motivation for drugs of abuse, and relapse-like behaviors. There is also a sex difference in the dopamine response in the nucleus accumbens. Ovariectomized female rats exhibit a smaller initial dopamine increase after cocaine treatment than castrated males. Estradiol treatment of ovariectomized female rats enhances stimulated dopamine release in the dorsolateral striatum, but not in the nucleus accumbens, resulting in a sex difference in the balance between these two dopaminergic projections. In the situation where drug-taking behavior becomes habitual, dopamine release has been reported to be enhanced in the dorsolateral striatum and attenuated in the nucleus accumbens. The sex difference in the balance between these neural systems is proposed to underlie sex differences in addiction.

 Dialogues Clin Neurosci. 2016;18:395-402.

Introduction

The chromosomes and hormones in the developing fetus contribute to sex differences in the brain.[1,2] The fact that we can find similar sex differences in the brains of humans and rodents suggests that the basic biology is different for females and males, and that not all sex differences in brain and behavior are due to sociocultural experiences that differ for men and women. This is true for sex differences in addiction, even though there are also effects of experience and culture on vulnerability to addiction that can differentially affect males and females.[3]

Engaging in pleasurable activities or eating sweet or highly palatable foods activate the reward system.[4,5] Drugs of abuse all produce their effects by causing changes in neurotransmitter function that increase neural activity in the reward system, and there are sex differences in this regard.[6-8] These ideas will be developed further below. Intriguingly, only about 10% to 16% of humans[9] and other species[10,11] become addicted to drugs. This is in spite of the fact that all individuals

Keywords: *addiction; amphetamine; cocaine; drug abuse; sex difference; substance use*

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Selected abbreviations and acronyms

D1DR	*D_1 dopamine receptor*
D2DR	*D_2 dopamine receptor*
DA	*dopamine*
DLS	*dorsolateral striatum*
DS	*dorsal striatum*
NAc	*nucleus accumbens*
OVX	*ovariectomized*

will exhibit long-term changes in the brain after being exposed to a drug of abuse.[12-14] In the laboratory, all rodents will eventually learn to self-administer cocaine or morphine if they are alone in a self-administration chamber for a few hours a day, but only about 10% to 16% of male rats will develop behaviors that are similar to the characteristics of addiction in humans.[10,11] Thus, even though there are changes in the brain in all individuals that receive a drug, the changes in the brains of those who become addicted are different from those who do not. Individual differences in genetics, personality traits, experiences during development, and whether one is male or female are all thought to contribute to how one responds to drugs or food or gambling and whether one develops compulsive behaviors associated with an addiction.

Sex differences in addiction-like behavior

Women who are vulnerable to addiction will tend to escalate use more rapidly to the point of addiction than men will. This is true for alcohol, most illicit drugs, and gambling.[6,15,16] In other words, for those women and men who are vulnerable to addiction, women escalate to addiction more rapidly than men. Similarly, in laboratory experiments, female rats acquire drug self-administration in an operant conditioning chamber more rapidly than male rats.[17-19] This is primarily due to circulating ovarian hormones in females, where short-term estradiol exposure enhances the rate of acquisition of drug taking.[19-24] In these laboratory experiments, subjects are trained to lever press or nose poke to receive an injection of a drug such as cocaine or morphine. Acquisition is measured by the number of days it takes for the animal to reach a stable level of responding for the drug. This animal model is useful for identifying factors that make an individual vulnerable to drug taking. The test for self-administration of drugs has inherent face validity for studying addiction. Using this behavioral test, female rats will also escalate drug taking more rapidly than males, and females will work harder than male rats to get a single injection.[25-29]

To examine motivation for a drug in the laboratory, animals are put on a reinforcement schedule that increases with each successive reinforcement delivered, a progressive ratio (PR) schedule that continues until the animals fail to complete the response requirement (referred to as the breaking point). Females exhibit a higher breaking point on a PR than males.[26,27,30] Estradiol treatment also enhances motivation in ovariectomized (OVX) rats.[31] These results suggest that estradiol is involved in the acquisition of and motivation for drug taking.

During attempts to quit (abstinence) use of drugs such as cocaine and amphetamine, women exhibit withdrawal symptoms that are more unpleasant than those of men.[32,33] Similarly, female smokers report increased negative affect during withdrawal and experience a greater stress response.[34] On the other hand, men exhibit greater withdrawal symptoms when quitting alcohol consumption.[35] During abstinence, women report greater craving induced by cues, and this is thought to result in greater vulnerability in women than in men, in terms of treatment outcomes.[36]

In studies with rodents, after self-administration is established, animals undergo an extinction process to examine the effect of abstinence on responding under conditions when the drug was previously available. During extinction, rats are placed in an operant chamber, but no drug is delivered even though the animal responds for the drug. This continues until the animal stops responding for drug. After that, the investigator examines both whether the animal will reinitiate self-administration and what increases reinitiation behavior. What is found is that there is greater drug-, cue-, and stress-induced reinstatement for cocaine and morphine in females than in males.[37-39] Reinstatement is also hormone-dependent in females, where estradiol enhances and progesterone attenuates reinstatement in females.[37,40-43]

Finally, although drug self-administration in laboratory animals resembles drug-taking behavior in humans, the animals do not show symptoms of addiction. More recent tests have been devised where animals exhibit symptoms more typically associated with addiction,

such as responding for drug even when not being rewarded, responding for drug in the presence of adverse consequences, high motivation to take drug on a PR schedule, and loss of motivation for previously desired reinforcers. Under conditions in which responding for drug can be assessed for these attributes, addiction-like behavior can be studied in the rat. Interestingly, only 10% to 20% of male rats exhibit addiction-like behavior, which is similar to the percentage of humans who become addicted.[10,44,45]

In the Becker laboratory, we use a choice paradigm where male and female rats are given a choice between palatable sugar pellets and intravenous cocaine. Early in the testing, all animals choose pellets, but after 3 to 7 weeks, a certain proportion of rats choose cocaine over pellets, and more females than males choose cocaine (*Figure 1*).[44,46] The rats that choose cocaine do so at the expense of the pellets that were previously found to be rewarding by these rats. Other laboratories have also found that more females than males choose cocaine over food reinforcement, and that this is not due to the dose of cocaine or the amount of food received.[47,48]

The reward system

The reward system is necessary for animals and humans to engage in behaviors such as eating, drinking, or mating.[7,49] Some of the key neurotransmitter projections of the reward system are illustrated schematically in *Figure 2*. Evidence for sex differences in the reward system has focused on the forebrain regions that receive input from neurons in the midbrain that use the neurotransmitter dopamine (DA).[8] This review will focus on the nucleus accumbens (NAc) and the dorsal striatum (DS). The NAc is important for engaging in behaviors and learning that they are rewarding,[50] whereas the striatum is involved in escalated drug taking and automatic or compulsive behaviors.[51] DA in the NAc and DS is important for the development of craving or "wanting"; the endogenous opiates in the NAc are important for the pleasure or "liking."[4,5] The feeling of pleasure associated with a drug may be transient, but wanting is not.[4,5] When use switches from being a casual pleasure to being avid and compulsive intake of the drug or food, the pattern of neural activation has shifted from the NAc to the DS.[51] Thus, addiction is associated with greater DA activation in the DS and reduced DA activity in the NAc.[52,53]

In the NAc and dorsolateral striatum (DLS), the activity of γ-aminobutyric acid (GABA)ergic medium spiny projection neurons is modulated by DA receptors D_1 and D_2 (D1DR and D2DR, respectively).[54-56] DA release activates D1DR-containing medium spiny neurons in the direct pathway and inhibits D2DR-containing neurons in the indirect pathway, collectively resulting in appetitive/approach responses.[57,58] Reduced DA release results in less inhibition of D2DR and attenuation of the ability to disrupt ongoing behavioral activities.[59,60] The direct pathway is important for initiation of appetitive behaviors, and the indirect pathway inhibits competing repetitive behaviors.[59,60] Within the striatum, plasticity in the direct and indirect pathways is thought to occur in opposite directions during addiction, with greater activation of the direct pathway driving motivated behaviors and reduced activity in the indirect pathway resulting in greater addiction-like behaviors, especially when the DLS becomes involved. This is referred to as "reciprocal plasticity," and it has been found to be associated with acquisition of goal-directed behavior in the dorsomedial striatum.[61]

In the laboratory, self-administration or repeated treatment with drugs such as cocaine, amphetamine, or morphine produce long-term changes in the structure and function of the neurons in the reward system.[12-14,62] Brain imaging studies in humans find DA release in the NAc is reduced in cocaine addicts,[63] and similar results are found in animal studies using in vivo microdialysis.[46,64] Next, the evidence indicating that sex differences in the organization of the reward system mediate important aspects of sex differences in addiction will be discussed.

Sex differences in the reward system

As noted above, there are sex differences in drug-taking behavior, and estradiol treatment is thought to mediate these effects in part. Estradiol has been shown to enhance the behavioral response to amphetamine and cocaine, as indicated by greater stereotypy, locomotion, and rotational behavior after OVX rats are treated with estradiol.[65-70] In OVX female rats, estradiol enhances acquisition of, escalation of, motivation for, and reinstatement of drug-taking behavior. These effects are thought to be mediated by the action of estradiol in DLS, where estradiol treatment of OVX female rats enhances the amphetamine- or cocaine-induced increase of DA in fe-

males, but not in males.[71,72] On the other hand, progesterone can attenuate the effect of estradiol to enhance acquisition of cocaine-taking behavior in female rats[20,73] and attenuates cocaine intake in women.[74,75]

A greater behavioral response to amphetamine and cocaine by females than by males is only part of the sex difference in the DLS. The behaviors exhibited are also different, and the neural response to amphetamine, as indicated by c-fos activation, is sexually dimorphic.[71,76] These findings suggest that the difference between males and females is not simply a quantitative difference, where females show a greater response than

Figure 1. Females are more likely to develop a preference for cocaine. **(A)** The development of cocaine preferences in male (open circles) and female (filled circles) rats (n =12 per sex). Significant increase in the proportion of cocaine-preferring (CP) females between the second and last fixed-ratio 5 (FR5) tests (*P=0.05). The proportion of CP females was greater than males ($P=0.05). **(B)** The stability of preferences in pellet-preferring (PP) rats and CP rats (both before and after CP developed). Significant difference between PP and CP rats within same preference category (#P=0.05). Significant difference in preference category before and after CP developed (*P=0.05). Significant difference between the "preference for cocaine" and "preference for pellets" categories within a given group (^P=0.05). PP rats (n = 16) and CP rats (n = 8). **(C)** Representative self-administration behavior in a PP rat over the 21 FR sessions, displaying the number of infusions (gray) and pellets (black) earned each day during the cocaine-only or pellet-only sessions (closed symbols) and the choice session (open symbols). **(D)** Representative self-administration behavior in a CP rat (CP criteria met on day 11 in this case).

males. The sex differences in the response to cocaine and amphetamine may also reflect different underlying neural mechanisms mediating the response to these drugs—a phenomenon referred to as a "divergent" sex difference.[3]

The increase in stimulated striatal DA release is a direct effect of estradiol on the striatum that is blocked by selected estradiol receptor antagonists.[77-79] However, estradiol receptors are not found on the striatal DA terminals, but are found on medium spiny GABA projection neurons that have reciprocal collaterals onto the presynaptic DA terminals.[80] These neuroanatomical results are consistent with patch-clamp electrophysiology showing that estradiol blocks L-type calcium channels in medium spiny striatal neurons and with in vivo microdialysis studies showing that estradiol attenuates potassium-stimulated striatal GABA release.[81,82] Thus, the rapid effects of estradiol on stimulated striatal DA release are apparently indirectly mediated by an attenuation of GABAergic inhibition.

In the NAc, the cocaine-induced increase in DA in OVX females is lower than the cocaine-induced increase in DA from NAc of male rats, with or without estradiol treatment.[71] A similar sex difference in rats has been reported in the NAc core DA response to amphetamine.[83,84] In nicotine-addicted humans, the ventral striatal DA response to nicotine is greater in men than women.[53] Thus, both the DLS and NAc exhibit different responses in males and females, and there are different processes mediating sex differences in DLS versus NAc regions. Interestingly, changes in glutamate function, associated with an addiction-like phenotype, are the same in males and females.[85]

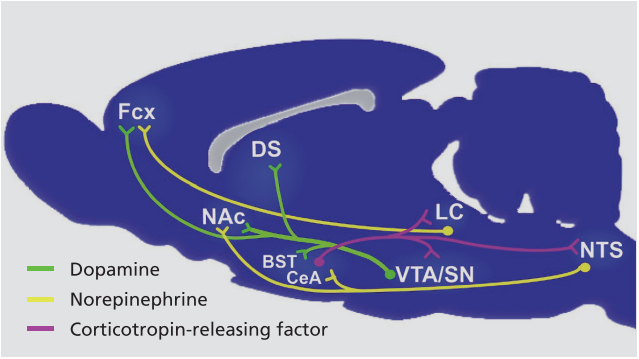

Figure 2. A sagittal section of the rat brain depicting some of the neural systems involved in the reward system. Not shown are the glutamate projections from frontal cortex and other brain regions, as well as the GABAergic neurons and the enkaphalin and dynorphin neurons in the nucleus accumbens and dorsal striatum. BST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DS, dorsal striatum; Fcx, frontal cortex; LC, locus coeruleus; NAc, nucleus accumbens; NTS, nucleus tractus solitarus; VTA/SN, ventral tegmental area/substantia nigra

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Male rats with lower NAc DA are more impulsive and more likely to develop addiction-like behaviors.[10,50] We find that, on average, females have lower NAc DA than males.[71] If both males and females that are found to have lower NAc DA are at greater risk of developing cocaine self-administration behavior and addiction-like behavior, then the sex difference in NAc DA release induced by cocaine may reflect a population difference. In other words, if more females have this characteristic than males, then it appears that females as a group are more at risk; the overall sex difference reflects the greater number of females than males with lower NAc DA. This still needs to be empirically determined and is currently under investigation in the Becker laboratory.

Expression of striatal D1DR is 10% higher in males than in females, and although there are no sex differences in D2DR densities, there is a sexually dimorphic effect of estradiol on D2DR, where estradiol rapidly downregulates D_2 binding in females, but not males.[86] In cell culture, pretreatment with estradiol reduces D2DR inhibition of adenylate cyclase activity and enhances D1DR activation of adenylate cyclase.[87,88] Additionally, estradiol treatment decreases expression of regulator of G-protein signaling 9-2 (RGS9-2), a GTPase-activating protein associated with D2DR signaling.[89]

It is proposed that females acquire the cocaine-taking behavior more rapidly than males and that they take more cocaine because there is less of an increase in DA/infusion in NAc. More cocaine is needed to achieve comparable increases in DA. We also suggest that the transition to compulsive drug taking in females is facilitated by enhanced DA transmission in DLS relative to NAc. It seems likely that in females, estradiol is involved in exacerbating the rate of escalation of drug taking by increasing the reinforcing effects of many drugs of abuse during the initial stages of acquisition and transition to addiction.

Implications for addiction treatment and other human conditions

These sex differences in the reward system and effects of estradiol on dopaminergic function in the DLS have implications for development of treatments for addiction, as well other psychiatric conditions. Even though estradiol enhances acquisition of drug taking and the transition to addictive-like behavior in rats, once animals are avidly self-administering cocaine, the estrous cycle does not modulate drug-taking behavior.[44,46] This suggests that ovarian hormones may be helpful as adjunctive treatments early in the acquisition of drug-taking behavior, before compulsive behavior develops, when progesterone may attenuate some of the subjective effects of drugs of abuse and thereby decrease drug intake.[20,75] Later in the addiction process, based on this model of addiction, drugs that restore the balance between the direct and indirect pathways in DS are most likely to be beneficial.

In terms of other disorders, it has long been noted that there are sex differences in schizophrenia, with women having later onset of symptoms and a slight increase in incidence associated with menopause,[90,91] leading to the suggestion that estradiol is protective in schizophrenia. This may seem counterintuitive if estradiol enhances stimulated DA release in the DS, as schizophrenia is thought of as a disorder associated with hyperdopaminergic activity. Most studies of the role of ovarian hormones in schizophrenia, using animal models, have focused on the possible antipsychotic effects of high doses of estradiol.[92,93] It should be noted that the effects of estradiol on drug taking and DA release discussed above are mediated by physiological doses of estradiol and that a high dose of estradiol downregulates presynaptic DA release.[77] On the other hand, estradiol is not the only hormone secreted during the menstrual cycle, and progesterone may also contribute to sex differences in schizophrenia.[90] Finally, we know that schizophrenia is not due solely to disordered DA function, and although the ovarian hormones may contribute to symptomatology in some way, it is yet to be determined whether it is modulation of DA function that mediates this effect.

Conclusions

Drug-taking behavior is thought to be initiated by the activation of the NAc and dorsomedial striatum, where the rewarding properties of the drug and the cues that predict the drug are first learned. It is proposed that the transition to compulsive drug taking is mediated by enhanced activation of DA release in DLS and by attenuation of the DA response in the NAc and dorsomedial striatum. Women exhibit more rapid escalation of drug taking to addiction, exhibit a greater withdrawal response with abstinence, and tend to exhibit relapse due to cue-induced craving more than men. In rodents, acquisition and escalation of drug taking, motivation for drugs of abuse, and relapse-like behaviors are greater in females than in males. Estradiol enhances these sex differences in females. In the drug-naive rat, there is a sex difference in the DA response in the NAc, with OVX females exhibiting a lower initial DA increase after cocaine treatment than castrated males. Estradiol treatment of OVX female rats enhances stimulated DA release in DLS, but not NAc, resulting in a sex difference in the balance between the NAc and DLS. It has been reported that when drug-taking behavior becomes habitual, enhanced DA release in the DLS and attenuated NAc DA release occur. The sex difference in the balance between these neural systems is proposed as a mechanism that mediates sex differences in addiction. ❑

Acknowledgments/Conflict of Interest: This work was supported by a grant from the National Institute on Drug Abuse to JBB (R01-DA-039952). The author declares no conflict of interest.

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