



Review

Sex differences in exercise and drug addiction: A mini review of animal studies

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Abstract

Growing literature has demonstrated that exercise may be an effective prevention and treatment option for drug addiction. In the past few years, many studies have suggested that there were sex differences in all phases of drug addiction. However, very limited research has investigated sex differences in the effectiveness of exercise intervention in drug addiction and rehabilitation. In this mini review, we summarize the effect of sex on the results of using exercise to prevent and treat drug addiction. The studies we consider span various animal models and use multiple types of exercise to examine the effectiveness of exercise on the neurobiological mechanism of exercise rehabilitation. We believe that exercise as an adjuvant intervention strategy can be applied better in drug addiction prevention and recovery.

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1. Introduction

Drug addiction, also known as substance dependence, is a chronic disorder characterized by the compulsion to seek and take a drug, loss of control in limiting intake, and emergence of a negative emotional state when access to a drug is prohibited. The neurobiology of drug addiction involves specific neuronal pathway dysfunctions and pathological neuropsychological dysfunctions.¹ Recent research has found that there are significant sex differences in many aspects of drug addiction, including its neurobiology mechanism.^{2–5} In general, males are more likely to engage in risky behavior that includes experimenting with drugs of abuse compared to

females, while females are more likely to begin taking drugs as self-medication to reduce stress or alleviate depression.⁶ In addition, sex differences in patterns of drug-cue exposure, severity, and outcomes of drug addiction have also been reported.^{7,8} Clinical studies also demonstrated that female subjects with substance dependence showed higher scores of approaching tendencies and more motor impulsivity than male individuals with drug dependence,⁹ and female addicts are more unwilling to take part in detoxification treatment.¹⁰ Moreover, studies of brain activation and subjective craving behavior showed that female cocaine users had a positive correlation between craving behavior and brain activation in the midbrain, hippocampus, ventrolateral prefrontal cortex, and thalamus, whereas male cocaine users showed the correlations between craving and activation in the dorsolateral, dorsomedial, temporal, and parietal cortices as well as in the hippocampus.⁷ In addition, studies also showed that female drug users are more likely to develop depression and anxiety than male subjects with drug addiction.^{11,12} The sex differences in drug addiction are also confirmed in animal studies. For example, female rats have higher levels of morphine and heroin intake than male rats, while female rats are more

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vulnerable and sensitive than males to the reinstatement of cocaine-seeking behavior.^{6,13,14} Both human and animal studies demonstrated that circulating levels of ovarian steroid hormones account for these sex differences, and that progesterone and allopregnanalone counteract the effects of estrogen and reduce drug seeking behavior in females.¹⁵

Recently, an increasing evidence indicates that exercise leads to positive results in drug addiction prevention and recovery.¹⁶ But few studies can elaborate on this phenomenon in more detail. We hypothesize that exercise may affect neuroplasticity and regulate the positive reinforcement of the drug through influencing the neurotransmitters system, cell-signaling molecules and its gene expression, epigenetics, neuroplasticity, and neurogenesis. In this review, we discuss the sex differences of addiction models, exercise intervention in drug addiction recovery and its underlying neurobiological mechanism. We believe that a better understanding of sex differences in exercise intervention in drug addiction prevention and recovery will provide a stronger theoretical basis for novel sex-specific rehabilitations.

2. Sex differences in animal model of drug addiction

2.1. Self-administration (SA) paradigm

The traditional animal models of drug abuse are framed by the behaviorist view that emphasizes the action of drugs as positive reinforcer, much like food, water, and other “natural” reinforcers. Studies showed that female rats go into stable SA behaviors more rapidly at a lower dose and are more sensitive to the positive reinforcement of drugs compare to male rats.¹⁷ The female animals are also likely maintaining higher drug intake throughout the SA extinction than males.¹⁸ In general, female animals learn to self-administer various drugs (cocaine, methylphenidates, and amphetamine) faster, and are more sensitive to the rewarding effects than males.¹⁹ Further research indicated that ovariectomized female rats showed the same craving behavior as males when reinstated by drug, slower acquisition, lower drug intake, and longer extinction in SA compared to intact female rats.^{17,20,21} Together, these studies suggested that ovary hormones, such as estrogens, play critical roles in the sex differences in drug addiction behaviors, such as acquisition, maintenance, craving, extinction, and reinstatement of SA in animals.

2.2. Conditioned place preference (CPP) paradigm

In addition to SA, CPP experiments provide additional information on the rewarding effects of drug abuse. As reported in SA, female rats required shorter training cycle and lower doses of the drug to acquire CPP compared to male rats.^{22, 23} This sex difference in CPP between female and male rats was observed in both adolescent and adulthood.²⁴ However, some studies showed controversial results in the gender effect on CPP. For example, studies reported no gender difference in CPP acquisition at a low or high dose of cocaine (3 or 25 mg/kg), except that female rats were more reinstated than

male rats.²⁵ At doses of morphine from 0.2 to 10.0 mg/kg, male and female rats showed the same level of preference for the drug-associated chamber, but when the dose was increased from 10.0 to 17.5 mg/kg, morphine lost positive reinforcer in males while female rats maintained a strong preference for the morphine-associated chamber at doses up to 30 mg/kg.²⁶ The controversial results in gender effects on CPP behavior are also associated with specific drugs and strain of animals. Studies reported that there was no sex difference in amphetamine induced CPP.^{27,28} Furthermore, studies of nicotine addiction showed a dose dependent CPP only in male rats, not in female rats.²⁹ On the other hand, there is a significant gender difference in morphine induced CPP in Wistar rats,³⁰ but not in SD rats.²⁶ In accordance with SA, the rewarding effect of drugs in CPP is also closely associated with ovary hormones. For example, ovariectomized female rats showed a reduction of cocaine induced CPP behavior compared to intact females.³¹

There were few studies about the effect of exercise only on CPP, but enough data suggest that rats find long term voluntary wheel running rewarding,^{32,33} which can develop and sustain significant CPP to brief periods or nightly,^{34,35} and also produce plasticity in the mesolimbic reward pathway like repeated exposure to drug or natural rewards.³³ Therefore, there may be sex differences in exercise's effect on drug based upon these animal models of drug addiction.

3. Sex differences in various types of exercises' effects on drug rehabilitation

In the animal experiments on drug addiction through exercise intervention, voluntary running wheel and forced treadmill running are the main modes of exercise. Running wheel is an active exercise and is widely used, while forced treadmill running is passive and less used.

Although exercising has been investigated as an intervention for drug addiction and rehabilitation, few studies have been done on the sex differences in the effectiveness of exercise on drug rehabilitation in animals. Sex differences in both wheel and treadmill running behaviors have been documented. For instance, female rats with drug addiction often run more laps (longer distance) in wheel exercise than males within the same time frame.^{36–39} In a 10-day forced treadmill running training, male rats developed small reduction of serum corticosteroid-binding globulin, which was not found in female rats,⁴⁰ suggesting a different physiological response induced by treadmill exercise in female and male rats. There were little studies about the psychological response between the two exercise models. Wheel running tended to attract individuals who are highly motivated to engage in frequent, sustained exercise, which reflected a voluntary, active physical and mental state, while treadmill running attracts those that are forced to exercise, which reflects an attitude towards exercise.⁴¹ Only very recently have there been studies demonstrating the sex differences in exercise intervention for drug addiction and rehabilitation. In one such study, Sanchez and colleagues⁴² found that 10-day wheel running after the formation of rat SA attenuated

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