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Sex differences in drug addiction and response to exercise intervention: from human to animal studies

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Abstract

Accumulated research supports the idea that exercise could be an option of potential prevention and treatment for drug addiction. During the past few years, there has been increased interest in investigating of sex differences in exercise and drug addiction. This demonstrates that sex-specific exercise intervention strategies may be important for preventing and treating drug addiction in men and women. However, little is known about how and why sex differences are found when doing exercise-induced interventions for drug addiction. In this review, we included both animal and human that pulled subjects from a varied age demographic, as well as neurobiological mechanisms that may highlight the sex-related differences in these potential to assess the impact of sex-specific roles in drug addiction and exercise therapies.

Keywords

Sex differences; Drug addiction; Exercise; Animal and human studies; Neurobiological mechanisms

1. Introduction

Drug addiction is often referred to as a chronic brain disorder characterized by compulsive and uncontrollable drug seeking tendencies and usage, paired with the emergence of a negative emotional state when drug access is prohibited (Wakefield, 2015; Leshner, 1997). The neurobiology of drug addiction involves dysfunctions in specific neural pathways and neuropsychological pathology (Levy, 2013; Koob and Volkow, 2010). Numerous clinical and preclinical studies have found that sex differences emerge throughout all phases of drug

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addiction (Franconi *et al.*, 2012; Becker and Hu, 2008; Anker and Carroll, 2011; Carroll and Anker, 2010). Studies of drug addiction in humans and animals have demonstrated that fluctuating levels of steroid hormones account for these sex differences. For example, estradiol facilitates positive subjective effects of drugs, while progesterone and its metabolite allopregnanolone attenuate drug-related responses and protect against the aversive effect of drugs in females (Becker *et al.*, 2012; Carroll and Anker, 2010). Similarly, testosterone has been shown to modulate drug-related awarding effects and behavioral response differently in males and females (Menendez-Delmestre and Segarra, 2011; Bawor *et al.*, 2014).

The most common treatments of drug addiction mainly involve pharmacological and social psychological approaches for symptom relief , not relapse prevention for drug addicts after detoxification (Winters *et al.*, 2014; Bailey and Husbands, 2014). However, many forms of pharmacological treatments can also be addictive and malevolent to patients. Therefore, there is an urgency to seek more effective approaches as adjunctive treatment of drug addiction. Recently, increasing evidence from human and animal experiments indicates that exercise may be an option in terms of potential interventions in the treatment of addiction. Studies have demonstrated that exercise can effectively reduce the susceptibility to and craving for addictive drugs, producing significant effects on drug addiction prevention and rehabilitation (Lynch *et al.*, 2013; Smith and Lynch, 2011; Zschucke *et al.*, 2012). Although few human studies have focused on sex and hormonal differences related to the efficacy of exercise at preventing and treating drug abuse, limited preliminary findings suggest that sex differences exist in the usage of exercise as a prevention and treatment method for alcohol, marijuana, and other illicit drugs (Korhonen *et al.*, 2009; Chen *et al.*, 2010; Pate *et al.*, 1996; Dolezal *et al.*, 2013). Animal studies also showed sex differences in a variety of substances, but the sex-bias effects of exercise on the treatment of some drug addiction cases have been controversial (Cosgrove *et al.*, 2002; Peterson *et al.*, 2014; Smith *et al.*, 2011; Smith *et al.*, 2012; Thanos *et al.*, 2010; Ehringer *et al.*, 2009; Sanchez *et al.*, 2014; Zlebnik *et al.*, 2014b; Zhou *et al.*, 2014). While there is no clear reason why men and women face drug addiction differently, extensive studies showed that sex hormones play critical roles in synaptic plasticity, neurogenesis and neurotransmitter systems which might be part of underlying mechanisms of drug addiction (Scarduzio *et al.*, 2013; Li *et al.*, 2011; Galea *et al.*, 2014; Barth *et al.*, 2015; Wetherington, 2010). As recently highlighted in Nature, men and women often have different profiles of drug safety and treatment efficacy (Pollitzer, 2013), we predict that men may experience different effects from exercises treating drug addiction compared to women. In order to elaborate on the sex differences in the benevolent effects of exercise-induced drug addiction treatment, in this review, we will discuss sex differences in drug addiction, exercise, the efficacy of exercise intervention for drug addiction, and its underlying neurobiological mechanisms. We believe that a better understanding of sex differences in exercise intervention for drug addiction prevention and recovery will provide a theoretical basis for novel sex-specific rehabilitations.

2. Sex differences in drug addiction

2.1 Animal studies

Sex differences in drug addiction have also been confirmed in animal studies, and this is reflected in laboratory animal models of drug addiction. The traditional animal models of drug addiction are framed by behavioral tests that emphasize the actions of drugs as positive reinforcers, such as the self-administration (SA) paradigm and conditioned place preference (CPP) paradigm. In the following sections, we will mainly discuss sex differences in the two commonly used animal models: SA and CPP.

As the most recognized animal model for evaluating various aspects of drug addiction, SA is highly correlated with human drug addiction behavior in humans (Panlilio and Goldberg, 2007; Henningfield *et al.*, 1991). Extensive literature has focused on sex differences in SA (Fattore *et al.*, 2008; Fattore *et al.*, 2009). Researchers found that female rats learn to self-administer various drugs (e.g., cocaine, methylphenidates, amphetamine and heroin) faster, and are more sensitive to the rewarding effects than males (Kerstetter *et al.*, 2008; Lynch and Carroll, 1999; Lynch, 2006). Moreover, female rats show a longer elevation of drug-seeking behavior during periods of abstinence and are more susceptible to the escalation of SA than males for cocaine, methamphetamine, cannabinoid and other illicit drugs (Roth and Carroll, 2004; Reichel *et al.*, 2012; Fattore *et al.*, 2010; Fattore *et al.*, 2009), and are also likelier to have higher drug intake for maintaining SA extinction and reinstatement compared to males (Fattore *et al.*, 2009; Lynch and Carroll, 2000; Fattore *et al.*, 2007). These sex differences in drug addiction are partially regulated by sex hormones. For example, during the estrus phase, female rats (endogenous estradiol level is high) have more active drug-seeking behavior and consume greater amounts of drug than rats in non-estrus phase (estradiol level is low) (Kerstetter *et al.*, 2008; Roth *et al.*, 2002). Such estrogen-facilitated effects of drug addiction were further evidenced by studies of ovariectomized rats that expressed reduced acquisition, attenuated drug intake and longer extinction in SA compared to intact female rats with no difference from male rats (Fattore *et al.*, 2007; Jackson *et al.*, 2006). Taken together, these studies suggest that ovary hormones play a critical role in female addictive behaviors, and that females express greater vulnerability than males to develop an addicted phenotype such as acquisition, maintenance, craving, extinction and reinstatement.

As a popular animal model of drug addiction, CPP assesses the rewarding effects of multiple addicted phenotypes by measuring the learning process of drug addiction, making it fundamentally distinct from SA (Napier *et al.*, 2013; Bardo and Bevins, 2000). CPP represents the conditioned reinforcing effects of drugs, which is closely related to environmental cues for drug craving behavior rather than the reinforcing effects of drugs or drug abuse behavior itself (Sanchis-Segura and Spanagel, 2006). Studies showed that female rats often required shorter training cycles and lower dosages of drugs (including cocaine, morphine, nicotine, methylamphetamine, etc) to acquire CPP compared to that in males (Russo *et al.*, 2003b; Randall *et al.*, 1998; Zakharova *et al.*, 2009; Chen *et al.*, 2003; Lenoir *et al.*, 2015; Carroll and Anker, 2010). However, some studies showed no sex differences in the training cycle for CPP acquisition (Mathews and McCormick, 2007; Schindler *et al.*,

2002; Hilderbrand and Lasek, 2014; Cummins *et al.*, 2013; Bobzean *et al.*, 2010). Such controversial findings can possibly be attributed to the type of drug, dosages of administration and age of the animals. Some other independent studies also reported that female animals needed higher dosage of drug (e.g., ethanol, nicotine, cocaine, morphine) to achieve CPP (Roger-Sanchez *et al.*, 2012; Torres *et al.*, 2009; Gioiosa *et al.*, 2008). Despite the inconsistent results regarding CPP between males and females, it is generally accepted that the rewarding effect of drugs in CPP is greatly associated with levels of ovary hormones in females since ovariectomized female rats showed a reduction of drug induced CPP behavior compared to intact females (Russo *et al.*, 2003a; Parada *et al.*, 2012; Torres *et al.*, 2009). Altogether, these contradicting results on sex effects related to CPP behavior are partially associated with drug types and dosages, animal species and ages, and the levels of steroid hormones.

Furthermore, most of drug addiction, withdraw and abstinence are associated with dysregulation of hypothalamic-pituitary adrenal (HPA) axis which directly associated with stress. While activation of HPA axis has been found to stimulate drug use and relapse, studies demonstrated that activation of ovarian hormone in females often have higher circulating levels of cortisol and greater release of adrenocorticotropic hormone in response to stress, while testosterone has been demonstrated to suppress the HPA axis in male rats (Bobzean *et al.*, 2014; Handa *et al*. 1994; Sinha 2008).

2.2 Human studies

It is generally accepted that women exhibit lower rates of drug abuse and addiction than men, although the total number of female addictive drug users has increased in recent years (Bobzean *et al.*, 2014). Indeed, men and women showed differences in the initiation and reasons for abusing drugs, drug-seeking and relapse during periods of abstinence, and treatment outcomes (Moeller, 2012; Kennedy *et al.*, 2013; Greenfield *et al.*, 2007; Becker *et al.*, 2012). For example, female subjects with drug addiction show higher levels of craving, behavioral activation and motor impulsivity in drug/cue exposure than male individuals with drug addiction (Perry *et al.*, 2013; Schlauch *et al.*, 2013), and women become dependent on drugs more rapidly than men (Hernandez-Avila *et al.*, 2004; Becker and Hu, 2008). Females are more inclined to begin taking drugs as self-medication to alleviate symptoms of mental disease (Becker *et al.*, 2012). Once addicted to a drug (i.e., opiates, nicotine, alcohol, cocaine and the psychomotor stimulants), females tend to have more difficulty giving up drugs and are at greater risk for relapse following abstinence compared to their male counterparts (Becker and Hu, 2008; Lynch *et al.*, 2002). Compared to male subjects in drug abuse treatment programs, female drug users often develop more severe withdrawal symptom, greater mood and anxiety disorders (Fox and Sinha, 2009; Doran, 2013; Back *et al.*, 2011), use more combinations of different drugs and legal psychoactive substances and have an unwillingness to participate detoxification program during the treatment (Kissin *et al.*, 2014; Ignjatova and Raleva, 2009; Bawor *et al.*, 2014). Increasing evidence suggested that sex hormone related brain organization and activities may contribute significantly to the differences in drug addiction between men and women. For example, endogenous estrogen promotes drug-induced reward behavior in females (Quinones-Jenab and Jenab, 2010; Anker and Carroll, 2011), and facilitates drug addiction through interaction with

dopaminergic system as well as opioid peptides (Segarra *et al.*, 2010; Jacobs and D'Esposito, 2011). In addition, it has been reported that men and women show differences in the associations between the type of drug addiction and body mass index (BMI). Examples include male alcohol abusers and drug addicts who often have a lower BMI, while females do not (Pickering *et al.*, 2011). Other studies also found that overweight men have higher rates of alcohol dependence and lower rates of nicotine dependence, whereas overweight women have lower incidence of alcohol dependence and higher risk for nicotine dependence (Vera-Villarroel *et al.*, 2014; Barry and Petry, 2009).

In summary, females are more vulnerable to drug addiction with faster initiation of addiction, higher intake of drugs, and more frequent relapses. Females are more sensitive to drug acquisition, escalation of drug intake, maintenance, withdrawal, reinstatement, relapse and treatment. Although controversial results on sex and drug addiction have been associated with drug types, dosages, animal species and ages, steroid hormone levels, and stress, further investigations on sex-specific effects in drug addiction on a large scale are needed.

3. Sex differences in exercise and fitness

3.1 Animal studies

The majority of animal studies on drug addiction intervention through exercise were performed in rodents with three different exercises models, including a voluntary running wheel, forced treadmill running and forced swimming (Table 3 & 4). Among these, the running wheel was the most popular mode of active physical exercise, while the other two modes of exercise were passive ones and might involve more stress.

Studies showed sex differences in all three types of exercise models. Females showed higher daily physical activity levels than males (Lightfoot, 2008). Moreover, a large number of studies showed that female rodents with drug addiction often ran more laps (longer distances) in wheel exercises than males within the same time frame (Eikelboom and Mills, 1988; Kanarek *et al.*, 2009; Smith *et al.*, 2011; Smith *et al.*, 2012), suggesting females and males may be endowed with different exercise intensity tendencies when presented with voluntary wheel running exercises. This difference may result partially from females having a higher locomotive efficiency as compared to males (Rezende *et al.*, 2006). Female mice have a greater capacity to increase their cardiac mass than males as an adaption in response to similar levels of exercises involving voluntary wheel running or even forced treadmill running (Konhilas *et al.*, 2004), suggesting that females are more inclined to increase exercise capacity and hypertrophic response to exercise. For passive exercise models, male rats showed a small reduction of serum corticosteroid-binding globulin that was not found in female rats during a 10-day forced treadmill running regimen (Brown *et al.*, 2007). It was also found that estrogen level increased in male rats muscle but not in females, while testosterone levels increased in muscle in both sexes after forced treadmill exercise (Aizawa *et al.*, 2008). This may be due to the factor that aromatase, an estrogen synthase, increases in males and decreases in females after acute exercise (Aizawa *et al.*, 2008). Compared to voluntary wheel running, which has reinforcing and rewarding properties, forced treadmill running is a more passive exercise and is commonly used for measurable interventions or

treatment (Belke and Wagner, 2005; Greenwood *et al.*, 2011; Brené *et al.*, 2007; Leasure and Jones, 2008). In terms of examining the rehabilitation effect of forced treadmill running on brain injury, a study found that slow continuous training is effective only in male mice, while more intense interval training produces results in females (English *et al.*, 2011). Sex differences in exercise performance are also observed in forced swimming. For instance, female rats are more active than males in water (Brotto *et al.*, 2000) and swim at faster speeds with less sign of fatigue (Birren and Kay, 1958; Kay and Birren, 1958). However, it is unclear if the sex differences in forced swimming are related to the gender-specific differences in the response to stress or if females favor swimming as an exercise. It is worth noting that the swimming model is also used to detect psychological status (e.g., anxiety, depression and stress), cognition processes (e.g., learning and memory), as well as an intervention in treating drug relapse and addiction (Segat *et al.*, 2014; Fadaei *et al.*, 2015).

To conclude, female mice seem to have developed greater cardiovascular benefits in response to voluntary wheel running or even forced treadmill running compared to males. For brain injury rehabilitation, males respond better to forced treadmill continuous training, while more intense interval training is needed in females. Since females and males perform very differently among these exercise modes, it is important to include the consideration of the sex-specific exercise effectiveness on drug rehabilitation in animal experiments.

3.2 Human studies

Sex differences have been reported in different exercise models, including traditional aerobic exercises (walking, running, swimming and ball sports with modulate intensity), anaerobic exercises (strength training with high exercise intensity), and body-mind exercises (Yoga, Tai Chi and Qigong with very mild physical and mental exercise). Among these, aerobic exercises are most commonly used for intervening drug addiction (Table 3 & 4), while body-mind exercise is becoming a very popular practice in improving cognition (Man *et al.*, 2010; Gothe *et al.*, 2014).

Research has provided abundant evidence for sex-specific exercise-induced improvements in psychological and physiological well-being. For example, an eight week aerobic exercise intervention promoted higher levels of pulmonary function (forced vital capacity, forced expiratory volume and peak expiratory flow) and aerobic performance (peak oxygen consumption) in male cardiac patients compared to females (Temfemo *et al.*, 2011). Another study found that the aerobic exercise-induced improvements in cardiovascular function were only seen in men, not in women, with particularly little benefit seen for postmenopausal women (Pierce *et al.*, 2011). Recent research also suggests that enhanced cardiovascular structure and function, such as the development of ventricular hypertrophy and increase in VO2max, is greater in males rather than females when induced by long-term endurance exercises (Howden *et al.*, 2015). However, other studies showed no sex differences in these exercise induced effects on a cardiovascular rehabilitation (Pina *et al.*, 2014), while others reported that exercise might be a more important preventive factor for cardiovascular disease in women than men (Morita and Okita, 2013). Some of these different exercise effects on health between men and women are associated with sex-specific physiology in general, such as levels of maximal oxygen uptake, heart size, peak cardiac output (Uth,

2005; Wong *et al.*, 2008; Winsley *et al.*, 2009), and types of muscle fiber (Storey and Smith, 2012; Harris *et al.*, 2012; Hicks *et al.*, 2001). In general, there are sex differences in aerobic exercise associated with health improvements in both healthy people and individuals suffering from various diseases. It is unknown whether there are sex differences in aerobic exercise intervention's effect on drug addiction. On the other hand, studies showed that men often show a higher level of anaerobic exercise induced maximal hypoxia tolerance and higher level of peak post-exercise blood lactate concentration compares to women (Hill and Vingren, 2014; Hill and Smith, 1993). Studies also found that women often have a lower basal metabolism rates than men after the long-term yoga practice, which is likely to reduced arousal (Chaya *et al.*, 2006). In addition, there some discrepancies in the prevalence, preference or attitudes about exercise between the sexes. For example, men are more likely to participate in more than one type of exercise for longer durations and more frequently than females (Stapleton *et al.*, 2014; Deaner and Smith, 2013). A recent study in China suggests that women are more likely to practice Tai chi and dancing, while men involve in walking and jogging (Birdee *et al.*, 2013). Moreover, studies showed that men are more likely to engage in team and/or combat exercises than women (Kirchengast, 2014; Deaner *et al.*, 2012).

Taken together, results imply that women receive more beneficial effects from doing aerobics and body-mind exercises while men developed better capacity of hypoxia tolerance through anaerobic exercises. A greater understanding of sex differences in these exercise types may provide insight toward developing more effective exercise approaches and sex-specific treatments for drug addiction.

4. Sex differences in the efficacy of exercise intervention for drug addiction

Although extensive evidence shows that males and females are different in each phase of drug addiction as well as in various exercise activities, it is unclear whether such sex differences also exist for exercise interventions in drug addiction. During the past few decades, increasing evidence has suggested that exercises attenuate drug-seeking behaviors during drug initiation, escalation, extinction, abstinence and relapse (Lynch *et al.*, 2013; Smith and Lynch, 2011). It is crucial to decrease the susceptibility to drugs (preventive effect) at an early stage of drug addiction and reduce the drug craving (therapeutic effect) at later stages in order to prevent relapse. Here, we will review recent studies on sex differences in the efficacy of exercise intervention for drug addiction from human trials and animal studies.

4.1 Animal studies

Although there are numerous studies on various exercise types for the prevention and treatment of drug addiction in animals, many of them recruited only one gender as shown in Table 1. The majority of the reports showed beneficial effects from voluntary and forced exercise activities as drug addiction prevention and treatment in male and female animal studies.

In an attempt to understand the sex differences in exercise-induced effects on drug addiction, limited studies included both genders and reported controversial findings as

shown in table 2. Female rats showed reduction in cocaine CPP after chronic forced treadmill exercise, while male rats showed completed inhibition of drug CPP after exercise (Thanos *et al.*, 2010). On the other hand, another study showed a reduction in alcohol consumption in female rats post-exercise, not in male rats (Ehringer *et al.*, 2009). Additionally, a different study showed an attenuation of cocaine SA under extended-access conditions after exercise in both sexes (Smith *et al.*, 2011; Smith *et al.*, 2012). In accordance with these results, a recent study found that a 10-day wheel exercise prior to alcohol exposure attenuated withdrawal-induced seizure susceptibility in both genders of rats (Devaud *et al.*, 2012). Altogether, whether sex differences in the preventive effects of exercise on drug addiction remains unclear and further investigation in both genders is needed.

Although Table 1 shows how the majority of the studies on the therapeutic effects of exercise on drug addiction are conducted on male animals, Table 2 displays how voluntary wheel running showed reduction in both male and female rats, with females being more sensitive to the wheel running-induced reduction of cocaine SA than males (Cosgrove *et al.*, 2002). This was supported by the discovery that female rats were more sensitive to the rewarding effects of the drug (Anker *et al.*, 2011). In terms of exercise types, some research found that wheel running exercise reduced nicotine-seeking in male rats while female rats showed attenuated nicotine-seeking behavior by both running or an environmental enrichment (Sanchez *et al.*, 2014). In addition, studies revealed that male rats showed a greater attenuation of cocaine-seeking with longer access to wheel running than that in females (Peterson *et al.*, 2014), voluntary exercise mitigated extinction responses and cocaine-primed reinstatement in females but not males (Zlebnik *et al.*, 2014b), and a 12-day wheel running exercise reversed the depressive-like behaviors in alcohol-exposed males, but not in females (Brocardo *et al.*, 2012). Taken together, therapeutic effects seem to also be influenced by sex, which may be associated with different drug addiction models and exercise types.

4.2 Human studies

As shown in Table 3 and Table 4, human studies from the past two decades (1995 to 2014) show that various exercises may have preventive and therapeutic effects on drug addiction that can then be tailored by sex, with exercise-induced prevention and treatment for addictive drugs mainly limited to alcohol, tobacco and cannabis. Interestingly, the majority of published single-gender studies exploring preventive effects of exercise on drug addiction focused primarily on men while women were more involved in therapeutic studies on drug addiction. As shown in Table 3, in consistent with animal studies, exercises provide prevention and treatment effects on various drug addictions, regardless of exercise duration, intensity and type. However, the single gender studies are not able to display the sex effect on the exercise-induced reduction of drug addiction. Moreover, in many inclusive gender investigations, majority of the studies do not analyze and address the potential differences in the effects of exercise on drug addiction on men and women (Sinyor *et al.*, 1982; Burling *et al.*, 1992; Correia *et al.*, 2005; Linke *et al.*, 2012; Hallgren *et al.*, 2014; Smelson *et al.*, 2013; Escobedo *et al.*, 1993; Collingwood *et al.*, 2000; Werch *et al.*, 2005; Charilaou *et al.*, 2009),

only limited reports have dissected the different impacts of exercise in drug addiction in men and women (Table 4).

Although the number of human studies on sex differences in exercise and drug addiction is limited, there were many researchers who paid attention to sex differences in the preventive effects of exercise on drug abuse (Table 4). Studies found a reversed relationship between drug dependence and exercise participation in both men and women (Rodriguez Garcia *et al.*, 2014), while some revealed a much stronger association between exercise and substance abuse in women than men (Kulig *et al.*, 2003; Strohle *et al.*, 2007; Korhonen *et al.*, 2009; Pate *et al.*, 1996), and others showed greater preventive effects of exercise on drugs in men than women (Pate *et al.*, 2000). Although the reasons behind these conflicting results remains unknown, it may be associated with the various demographic backgrounds of subjects, different types of addictive drugs, as well as different exercise activities (Aaron *et al.*, 1995; Moore and Werch, 2005). Due to the limited number of human studies on sex differences in exercise intervention on drug addiction, it is still too early to provide a conclusive advice on gender-specific exercise recommendation for drug addiction prevention. Therefore, it is critical to extend further studies on exercise prevention in drug addiction in men and women, particularly in young populations when drugs are first introduced.

Exercise also showed sex-specific therapeutic effects on drug addiction as shown in Table 4. In only three studies that emphasized the potential sex specificity of exercise and drug addiction, data showed that long-term routine aerobic exercises reduced the risk of smoking, particularly in young men (Horn *et al.*, 2011), and enhanced recovery from methamphetamine dependency in men. However, the study failed to show these results in women (Dolezal *et al.*, 2013). Qigong, a typical body-mind exercise has been used as meditation therapy to reduce anxiety levels and withdrawal symptoms which are more common and severe in female substance abusers than males. Interestingly enough, individuals who maintained strong, disciplined mediation often had greater reductions in craving, anxiety, and withdrawal symptoms than those who practiced poor meditation (Chen *et al.*, 2010) The study suggests that female drug abusers might be more sensitive to the meditative therapy then males since females often suffer more anxiety disorders and express more severe withdrawal symptoms, and that the quality of Qigong meditation practice could be associated with intervention in withdrawal symptoms. These limited findings of sex differences in exercise intervention in drug addiction treatment seem to suggest that men and women may have different responses to the therapeutic effects of exercise on drug addiction depending on type of exercises and addictive drugs.

5. Underlying neurobiological mechanisms for the sex-specific efficacy of exercise intervention for drug addiction

Long-term drug abuse led to corresponding compensatory changes in various neuronal functions, particularly the mesolimbic dopamine reward system (Feltenstein and See, 2013), including a series of molecular events induced by multiple neurotransmitters and their receptors in the ventral tegmental area (VTA), nucleus accumbens (NAc) and prefrontal cortex (PFC) (Nestler, 2004). These changes result in the impaired reward network

processing, such as an addicted state, inhibitory feedback control and motivation (Baler and Volkow, 2006). On the other hand, there is considerable evidence that exercise can induce changes in neuroplasticity and regulate drug reward processing via the mesolimbic reward pathway (Zlebnik *et al.*, 2014a; Greenwood *et al.*, 2011; Werme *et al.*, 2000; Werme *et al.*, 2002b). Above all, the effects of drug addiction and exercise on these reward network signaling molecules are sex-dependent and regulated by steroid hormones (Miladi-Gorji *et al.*, 2014; Berchtold *et al.*, 2001; Peterson *et al.*, 2014; Lynch *et al.*, 2002; Becker and Hu, 2008). In this section, we present a brief overview of the sex differences in neural changes underlying the efficacy of exercise in drug addiction as indicated in Figure 1.

5.1 Synaptic plasticity and neurogenesis

5.1.1 Synaptic plasticity—Addictive drugs produce maladaptation via the mesocorticolimbic DA system, which includes changes of synaptic reorganization and synaptic function, such as long-term potentiation (LTP) and depression (Russo *et al.*, 2010; Luscher and Malenka, 2011; Kauer and Malenka, 2007; Kalivas and O'Brien, 2008). Much research has been done on sex differences in synaptic plasticity. In general, normal female rats have higher densities of dendritic spines and large spines in the NAc than males (Forlano and Woolley, 2010). In animal models, female rats with cocaine addiction had higher densities of the spine density and spiculate protuberance of medium spiny neurons in NAc during abstinence compared to males (Wissman *et al.*, 2011), the association between changes of dendritic spine plasticity and addicted behaviors was only found in females (Wissman *et al.*, 2011). In addition, compared to males, female rats demonstrated higher sensitivity to drug-induced LTP deficits (An and Zhang, 2013), which can be modulated by sex hormones as an underlying synaptic plasticity through direct interaction with membrane receptors for estrogens and androgens in rats (Scarduzio *et al.*, 2013), while a estradiol levels are higher in the female hippocampus compared to male animals (Brandt *et al.*, 2013). Furthermore, studies also demonstrated that brain structure and synaptic formation/plasticity is highly dependent on ovary hormones, particularly estrogen, but are less dependent on testosterone (Bobzean *et al.*, 2014; Mirbaha *et al.*, 2009; Evans and Foltin, 2010). These results suggest that addictive drugs regulate synaptic plasticity differently in men and women, which may be related to sex hormones.

Although there is no direct evidence of sex differences between exercise and drug addiction-induced impairment of synaptic plasticity, it is well known that exercise alone induces modified synaptic plasticity and reorganization by triggering the producing of brain derived neurotrophic factor (BDNF) and insulin-like growth factor 1 in the hippocampus, interfacing with the regulating balance between the glutamatergic system and the GABAergic system, which together mediate neuronal excitability and synaptic transmission to enhance cognitive function (Gomez-Pinilla and Hillman, 2013; Wu *et al.*, 2008; Farmer *et al.*, 2004). In addition, voluntary exercise also stimulates histone deacetylase and DNA demethylation of BDNF promoter IV to regulate brain plasticity by engaging mechanisms of epigenetic regulation (Gomez-Pinilla *et al.*, 2011). Recent studies found that short-term exercise enhanced hippocampal LTP and cognitive functions as well as increased numbers of spike LTP in morphine-dependent rats (Miladi-Gorji *et al.*, 2014). Moreover, the 30-day intensive treadmill exercise increased dendritic spine density and arborization in mouse striatal,

reducing drug-induced cognitive deficit (Toy *et al.*, 2014). Altogether, it is theoretical possible that exercise-induced neuronal protective roles in drug addiction may be mediated partially by promoting synaptic plasticity, and we speculate that sex-specific neuroplasticity may be an underlying basis for the efficacy of exercise in treating drug addiction between men and women.

5.1.2 Neurogenesis—Animal studies have shown that females have high levels of cell proliferation in the dentate gyrus of the hippocampus, which is mediated by natural fluctuations of gonadal hormones, compared to their male counterpart (Tatar *et al.*, 2013; Galea *et al.*, 2013; Galea, 2008; Bowers *et al.*, 2010). This kind of sex-specific neurogenesis in the hippocampus was also confirmed by other studies which reported that repeated exogenous estradiol administration altered neurogenesis and cell death in females, but not males (Barker and Galea, 2008). It was also reported that estradiol-induced neurogenesis and neuroprotection depended on the activation of either estrogen receptor subtype within the brain (Nilsen *et al.*, 2000; Suzuki *et al.*, 2007; Saleh *et al.*, 2013). Young male rats showed delayed neurogenesis in the hippocampus after repeated exposure to cannabinoid compared to young female rats (Lee *et al.*, 2014). Many studies have demonstrated that exercise can reduce the symptoms of drug addiction by ameliorating cognitive decline via the promotion of neurogenesis and activation of new neurons in the hippocampus. Such exercise-induced improvements of cognition were found more prominent in females than that in males (Engelmann *et al.*, 2014; Leasure and Nixon, 2010; Chow *et al.*, 2013). These differences in neurogenesis might be partly due to female animals having lower baseline values in terms of the number of newly proliferated cells and neuroblasts compared to males (Tzeng *et al.*, 2014). Although exercise can reduce the symptoms of drug addiction by ameliorating cognitive decline via the promotion of neurogenesis, there is little direct evidence specifically focusing on sex differences in exercise-induced neurogenesis or exercise intervention on drug addiction.

Studies have shown that repeated exposure to addictive drugs causes the suppression of neurogenesis and enhancement of apoptosis in specific brain regions, which contribute to the formation of drug-taking or drug-seeking behaviors as well as future relapse (Engelmann *et al.*, 2014; Mandyam *et al.*, 2007; Noonan *et al.*, 2010). Conversely, increased neurogenesis or gliogenesis in the brain's reward system may help reduce the vulnerability to relapse and promote recovery (Mandyam and Koob, 2012). Exercise has emerged as a potent intervening strategy for increasing neurogenesis and reducing apoptosis in mesocorticolimbic regions of brain, which promotes neuron health and reduces the risk of drug-related craving, mood disorders and cognitive impairment (Yau *et al.*, 2014; Cotman *et al.*, 2007; Maynard and Leasure, 2013; Engelmann *et al.*, 2014; Mandyam *et al.*, 2007; Leasure and Nixon, 2010). One study reported that treadmill running induced a higher level of neurogenesis and lower cell survival rate in the hippocampus of male mice compared to the female mice (Ma *et al.*, 2012). However, it is unclear whether such a male favored exercise effect on neurogenesis is associated with sex hormones (Aizawa *et al.*, 2008). Therefore, further investigations are needed for understand the sex differences in drug-related or exercise-induced neurogenesis in order to adequately develop sex-specific intervention on drug addiction.

5.2. Neurotransmitters and receptors

5.2.1. Dopamine and its receptor—Differing distributions of dopamine neurons in specific brain regions of animals have been observed between males and females. For example, male rats have more dopamine neurons in the substantia nigra, while females have more in the VTA and caudate nucleus (McArthur *et al.*, 2007). Likewise, females have significantly higher levels of dopamine in the PFC, while males have higher levels of dihydroxyphenylacetic acid (dopamine metabolite) (Duchesne *et al.*, 2009). This could be related to the fact that dopamine neurotransmission in the female rat is more tightly regulated by autoreceptors and transport in metabolic processes (Festa *et al.*, 2004; Walker *et al.*, 2006). In this way, dopamine receptors also appear to share similar characteristics. Male rats have 10% more DAR1 in the striatum and NAc than females (Becker and Hu, 2008), while females have few DAR2 in the striatum (Pohjalainen *et al.*, 1998). Meanwhile, some research indicates that sex differences in the dopaminergic system are influenced by gonadal hormones. For example, in female rats, estrogen enhances dopamine release and dopamine-mediated behaviors by acting on the striatum and accumbens rapidly and directly, but this is not the case in males (Becker, 1999). Additionally, the reduction of endogenous sex hormones in castrated or ovariectomized rats showed a lessening of amphetamine-induced dopamine release (Becker and Hu, 2008; Becker, 1999). Moreover, estrogen receptors (ERs) including α and β subtypes are both important for sexual differentiation of the brain, and the proportion of the two subtypes regulate the expression of TH mRNA, which controls dopamine levels in the brain. Pendergast and colleagues found that female rodents had the same levels of ERα mRNA as males in the locus coeruleus, whereas ERβ mRNA expression was significantly lower compared to males (Pendergast *et al.*, 2008), suggesting brain regional expression of ERs may contribute to sex differences in the dopamine system.

Although there is no direct evidence of sex differences related to dopamine and receptors mediating the efficacy of exercise in drug addiction, it is well documented that chronic exposure to addictive drugs results in the maladaptation of the mesolimbic dopamine reward circuitry, including the decrease of synaptic dopamine transporter (DAT) reuptake, increase of dopamine concentration, increase of levels of dopamine receptors 1 (DAR1) mRNA, decrease of levels of dopamine receptors 2 (DAR2) mRNA, and the increase of levels of tyrosine hydroxylase (TH) mRNA, a key limited enzyme in the synthesis process of dopamine (Volkow *et al.*, 2007; Leyton and Vezina, 2014; O'Dell *et al.*, 2012; Brenhouse *et al.*, 2008; Ikemoto and Bonci, 2014). Exercise also up-regulates DAR1 signal transduction, down-regulates the level of DAR2 mRNA in the NAc (Foley and Fleshner, 2008; Greenwood *et al.*, 2011; Roberts *et al.*, 2012; Toy *et al.*, 2014), reverses dopamine release and reduces the levels of TH expressing dopamine neurons in the midbrain, which is involved in ameliorating withdrawal symptoms and preventing relapse (Sobieraj *et al.*, 2014; Chen *et al.*, 2008). Based on this data, exercise can affect dopaminergic signaling at various levels, underlining its ability to reduce the susceptibility and craving for addictive drugs, and highlighting the possibility of a potential sex difference in exercise intervention for drug addiction via the dopamine system.

5.2.2 Endocannabinoids and their receptors—Endocannabinoids (eCBs), as a retrograde messenger, modulate the reward, motivation and relapse in drug addiction mainly through the activation or blockade of cannabinoid receptor 1 (CB1) (Bilbao, 2013; Friemel *et al.*, 2014; Vlachou and Panagis, 2014). Studies in humans and rodents have shown evidence that females are more sensitive than males to the effects of cannabinoid. For example, female rats have shown more severe withdrawal symptoms, including motor activity dysfunction, anxiety and depression, which may be a reflection of differences in the eCBs system (Fattore and Fratta, 2010; Craft *et al.*, 2013). The mechanisms underlying sex differences in cannabinoid effects appear to be associated with ovarian hormones, sexual dimorphism of the eCBs system and hypothalamic pituitary adrenal axis-eCBs interaction (Craft *et al.*, 2013). For instance, intact female rats have lower levels of the CB1 binging in the hypothalamus and PFC, but higher levels in the amygdala than ovariectomized females and intact males (Riebe *et al.*, 2010; López, 2010; Castelli *et al.*, 2014). This suggests that the eCBs system is modulated by ovarian hormones. Moreover, early life stress such as maternal deprivation can alter the eCBs system to participate in the motivation and reward for drugs, which significantly downregulates CB1 levels in the male rats' hippocampus, and upregulates CB1 receptor levels in the female hippocampus (Llorente-Berzal *et al.*, 2013; Reich *et al.*, 2009). In addition, male and female mice bred for high levels of voluntary wheel running differ from one another in response to antagonizing the CB1 receptor. For example, after injecting an antagonist of the CB1 receptor, male mice bred for high levels of voluntary wheel running showed a reduction of wheel revolutions over the entire period (10-120 min post-injection time), whereas their female counterparts showed a similar reduction only 70-120 min after injection (Keeney *et al.*, 2012). This limited circumstantial evidence suggests a possible sex difference in eCBs system.

Recent studies showed that CB1 regulates the functional balance between GABAergic inhibitory and glutamatergic excitatory synaptic inputs into VTA and NAc, which modulates dopaminergic activity to establish the addictive processes (Maldonado *et al.*, 2006; Mereu *et al.*, 2013). Most studies reported that the primary rewarding effects and the motivation to seek different drugs of abuse were attenuated by the inactivation of CB1 (Maldonado *et al.*, 2006; Maldonado *et al.*, 2013). Exercise has also shown to be a positive impact on the eCBs system. For example, a large number of human studies and animal experiments have shown that moderate or high intensity exercises could increase the circulating levels of eCBs, which mediated some physiological and psychological adaptations (i.e., analgesia, sedation and a sense of wellbeing) (Sparling *et al.*, 2003; Dietrich and McDaniel, 2004; Raichlen *et al.*, 2013; Heyman *et al.*, 2012). Animal studies have demonstrated that voluntary wheel running enhances the sensitivity of CB1 receptor stimulation to glutamate and GABA synapses in mice striatum for regulating the central reward pathway, and also increases the levels of CB1 in rat hippocampus for exercise-induced enhancement of progenitor cell proliferation (Hill *et al.*, 2010; De Chiara *et al.*, 2010). Furthermore, endocannabinoid signaling can be regulated by aerobic exercise and contributes to improving spatial memory (Tantimonaco *et al.*, 2014; Ferreira-Vieira *et al.*, 2014). The exercise-induced up-regulation of eCBs signaling involves neurogenesis, anti-apoptosis and synaptic plasticity (Tantimonaco *et al.*, 2014), spatial memory improvement and BDNF expression in the hippocampus (Ferreira-Vieira *et al.*, 2014), with possible implication for reward, depression

and mood (Heyman *et al.*, 2012; Tantimonaco *et al.*, 2014). Based on the key role of eCBs in drug addiction, exercise-induced changes of eCBs signaling may contribute to exercise's ability to prevent and treat drug addiction.

5.2.3 Other neurotransmitters and receptors—Besides dopamine and the eCBs neurotransmitters described above, sex differences were also found in the endogenous opioid system (EOS), GABAergic system and glutamatergic system. Recent studies showed that female mice express higher level of dynorphin in striatum (Chen *et al.*, 2009), whereas greater expression of proenkephalin mRNA in striatum and NAc was found in males (Torres-Reveron *et al.*, 2007). Female mice also had higher levels of dynorphin and enkephalin immunoreactivity in the hippocampus compared to males (Van Kempen *et al.*, 2013). The basal levels of dynorphin and enkephalin in the NAc, caudate putamen, and hippocampus varied during various phases of estrous cycle in female mice and rats (Roman *et al.*, 2006; Van Kempen *et al.*, 2013). For example, the levels of dynorphin and enkephalin immunoreactivity in rats are increased when estrogen levels are elevated (Torres-Reveron *et al.*, 2008; Torres-Reveron *et al.*, 2009). In addition, it is well known that women with opioid addiction have worse functional impairment, more psychiatric severity, and higher likelihoods of using opioids to cope with negative affect and pain than men (McHugh *et al.*, 2013; Kennedy *et al.*, 2013). However, animal studies showed that male mice had higher levels of expression of the morphine withdrawal symptoms than females, because GABA agonist baclofen attenuated morphine withdrawal signs observably only in females through reestablishing mu-opioid receptor binding sites (Diaz *et al.*, 2006). In addition, previous evidence showed that GABA(A) receptors subunit genes might preferentially contribute to methamphetamine use disorder in women, but not in men (Lin *et al.*, 2003). On the other hand, a very recent study found that metabotropic glutamate receptor 5 (mGluR5) activation is critical for the estradiol's impact on cocaine-induced behavioral sensitization in female rats (Martinez *et al.*, 2014), suggesting the glutamatergic system may involve different behavioral responses to cocaine between males and females. Investigations also showed that chronic ethanol exposure increased three NMDA receptors subunits (NR1,NR2A and NR2B) levels in male rats hippocampus, but not in females (Devaud and Alele, 2004). These limited studies suggest a possible gender difference in EOS, GABAergic system and glutamatergic system.

In animal studies, addictive drugs increased the release of dopamine directly by activating opiate receptors in the NAc, indirectly inhibiting GABAnergic interneuron or enhancing glutamategic signal in the VTA (Nestler, 2005). These neurotransmitters are also regulated by exercise to improve psychological status and cognitive function related to brain health (Ma, 2008). Among these signal molecules, the endogenous opioid system is a common substrate in drug addiction (Trigo *et al.*, 2010). Long-term active and passive exercise was able to increase the levels of endogenous opiate and their receptors (μ, δ, κ) in rats' plasma and hippocampus, especially endogenous β-endorphin and its μ receptor (Chen *et al.*, 2007; de Oliveira *et al.*, 2010). A previous study reported that 6-week wheel running exercise reduced the physiological dependence and sensitivity of the central opiate receptor to opiate receptor agonist in rats (Smith and Yancey, 2003). Studies have also shown that forced and voluntary running decrease glutamate concentrations and increase GABA concentrations in

the striatum and hippocampus (Jia *et al.*, 2014; Guezennec *et al.*, 1998; Biedermann *et al.*, 2012), reduce the mRNA levels of mGluR5, NMDA and GABAA receptors in a rat model of cerebral ischemia or in a mouse model of Alzheimer's disease (Zhang *et al.*, 2010; Revilla *et al.*, 2014). This raises the possibility that exercise promotes plastic changes in glutamate receptors and GABA receptors. Therefore, exercise may have the ability to reduce drug craving by regulating the endogenous opioid system, and normalizing the levels of glutamate and GABA and their functioning. However, further research is needed to focus on sex differences in EOS, GABAergic system and glutamatergic system between exercise intervention and drug addiction.

5.3 Transcriptional factors

Altered patterns of gene expression are considered a pervasive mechanism by which drugs of abuse can produce a state of addiction. There are two key transcription factors to coordinate gene expression, including CREB and ΔFosB. The sex differences exist in the regulation of gene expression by these transcription factors.

5.3.1 CREB—Much progress has been made in recent years to the examined sex differences in CREB-BDNF signaling. One study showed that there was no sex difference in basal phosphorylation CREB (pCREB) protein levels in the rat NAc, but that cocaine administration-induced elevation of pCREB level in the NAc was higher in females than males (Nazarian *et al.*, 2009). Other research showed that the levels of pCREB in the PFC increased in cocaine treated male rats, but not in female rats, which were positively correlated to CPP scores (Nygard *et al.*, 2013). These conflicting results may be due to different brain regions. Moreover, previous research has found that male mice with deleted BDNF genes in the forebrain exhibit hyperactivity but normal depression-related behaviors, while females display normal locomotor activity but a striking increase in depression-like behavior (Monteggia *et al.*, 2007). There is little research to elaborate the sex differences in other addictive drugs.

Earlier reports have shown that abnormal levels of BDNF within mesolimbic dopaminergic system may progressively facilitate the incubation of drug craving after prolonged withdrawal periods (Grimm *et al.*, 2003; Wang *et al.*, 2013; Ghitza *et al.*, 2010). Both wheel running and treadmill exercise can enhance the activity of CREB to increase mRNA levels of BDNF in the rat hippocampus (Vaynman *et al.*, 2003; Chen and Russo-Neustadt, 2005; Ji *et al.*, 2014). Further research has found that exercise during chronic exposure to morphine ameliorated rats' cognitive deficits and diminished the severity of dependency by up-regulating CREB-BDNF signaling (Miladi-Gorji *et al.*, 2011). A very exciting line of research uncovered that repeated exposure to cocaine increased BDNF exon IV expression in the PFC. It also stipulated that wheel running during abstinence on subsequent cocaine-seeking can attenuate this increase dose dependently, while the efficacy of exercise was inversely associated with BDNF exon IV expression (Peterson *et al.*, 2013). Furthermore, one human study demonstrated that exercise-induced elevation of serum BDNF concentration was more pronounced in men than in women (Schmidt-Kassow *et al.*, 2012). Differences in CREB-BDNF signaling could partly be due to the regulation of gonadal steroids (e.g., progesterone, estradiol and testosterone) in the peripheral and central nervous

system of human subjects and rodents (Pluchino *et al.*, 2013). For example, estradiol could promote pCREB levels (Cheong *et al.*, 2012). In particularly, fluctuating levels of estrogen along with the menstrual cycle affects CREB-BDNF signaling in the PFC and hippocampus, which have been implicated in the regulation of substance use disorders (Luine and Frankfurt, 2013; Carbone and Handa, 2013; Kuipers *et al.*, 2013). In summary, the above results demonstrate that exercise-induced changes of CREB-BDNF signaling are likely to improve some drug addiction-induced deleterious behaviors, and CREB-BDNF signaling is different in males and females that exercise or are addicted to drugs. Whether the drug or exercise related CREB-BDNF signaling could be a sensitive target for developing new intervention on sex-specific treatment feature for drug addiction requires further investigations.

5.3.2 Immediately Early Genes—Among the many immediately early genes (IEGs) known to influence the addiction process, ΔFosB and cFos are classic molecular markers for long-term adaptation in brain reward pathways, especially in the striatum (McClung *et al.*, 2004; Nestler, 2008). In regard to sex differences in Fos family protein, previous studies have shown that male rats expressed significantly higher levels of Fos protein within various brain regions during brain development (Olesen and Auger, 2005). A study using cocaine-induced CPP paradigm showed that female rats had a greater increase in caudate putamen ΔFosB levels than males (Nygard *et al.*, 2013). Moreover, a very recent study revealed that acute administration with methamphetamine caused a greater activation of c-Fos receptor-positive cells in male mice than females in the hippocampus (Zuloaga *et al.*, 2014). Gonadal hormones may be a major factor in these disparities, given that testosterone and estradiol induce Fos gene expression in adult and developmental rat brains, which are mediated by the binding of estrogen receptors (Giannakopoulou *et al.*, 2001; Olesen and Auger, 2005). In addition, some studies have found that exercise-induced estrogen increases in OVX rats contributed to the improvement of emotional and cognitive disorders, which were induced by the lack of estrogen (Ben *et al.*, 2010; Lu *et al.*, 2014). These findings imply that exercise may alter levels of the sex hormones to influence Fos gene expression differently in males and females.

However, there are few studies on the sex differences of IEGs related to exercise. Research has found that chronic voluntary wheel running was rewarding and elevated the protein levels of ΔFosB in rat and mice NAc and striatum, which might reduce the frequency and severity of substance abuse disorders (Werme *et al.*, 2002b; Greenwood *et al.*, 2011). Housing mice in enriched environments with 30-day voluntary wheel running during forced abstinence completely eliminated behavioral sensitization and CPP to cocaine, and dramatically reduced the protein expression of c-Fos in the core of NAc and the infralimbic cortex (Solinas *et al.*, 2008), which was in line with the results from cocaine SA in rats (Thiel *et al.*, 2010). Collectively, these findings demonstrate that exercise may serve as a substitute or competition for drug abuse by changing ΔFosB or cFos immunoreactivity in the reward system to protect against later or previous drug use. Moreover, animals studies showed that sex differences in dopamine receptors and the protein levels of pCREB induced by addictive drugs indirectly influence the expression of Fos protein (Gross and Marshall, 2009), suggesting that sex differences in the transcription factor CREB and

neurotransmitters system may contribute to sex differences related to Fos. Thus, sex differences in IEGs are likely to be involved in drug addiction and exercise.

6. Conclusions and future directions

As briefly reviewed above, a large number of human and rodent studies clearly show that there are sex differences in drug addiction and exercise. The sex differences are also found in the effectiveness of exercise on drug addiction prevention and treatment, as well as underlying neurobiological mechanisms. The postulate that exercise serves as an ideal intervention for drug addiction has been widely recognized and used in human and animal rehabilitation. Any sex differences in the efficacy of exercise intervention on drug addiction and rehabilitation remain understudied. Despite a small increase in animal research paying attention to how sex differences in the effectiveness of exercise reduce relapse vulnerability, little information is available to examine whether this effectiveness differs by sex among human subjects. The majority of the current studies were not inclusive and were performed on one gender, specifically males. As a recent article published in *Nature* by Pollitzer indicated, sex differences exist not only in basic cell biology, but also in clinical research, including research on drug effectiveness and side effects (Pollitzer, 2013). An important survey documenting the ratios of male-only versus female-only studies reported results that range from 3.7:1 in physiology to 5:1 in pharmacology and neuroscience (Beery and Zucker, 2011). Repeated attempts have been made to draw attention to the sex-dependent effects of exercise intervention on drug addiction, but the majority of human and rodent researchers still continue to use males exclusively for drug addiction and exercise studies. Thus, the tendency to ignore sex differences in human and rodent studies may limit the development of effective exercise intervention on drug abuse. Taken together in this review, we specify sex differences in types of various drug addictions, and exercise activities. We first discussed the different effects of active and passive exercise on drug rehabilitation among human and rodent subjects together. Then, we specifically summarized the preventive and therapeutic effects of exercise on drug addiction in human and animal studies. Lastly, we conducted deep speculation on several potential mechanisms that are the foundation for these differences, ranging from diversified molecular events induced by neurotransmitters and their receptors to neuroplasticity and neurogenesis.

To further understand the exercise conditions that most effectively reduce drug craving, we should consider the sex differences in drug addiction and exercise intervention between human and animal addicts. In particular, more studies on the neurobiological mechanism of exercise and its roles in preventing and treating drug addiction are needed.

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Highlights

- sex differences in drug addiction from human to animals,
- sex differences in exercise-based intervention to prevent and treat drug addiction from ***human to animal models***
- potential signal transduction pathways in exercise-based intervention in preventing and treating drug addiction

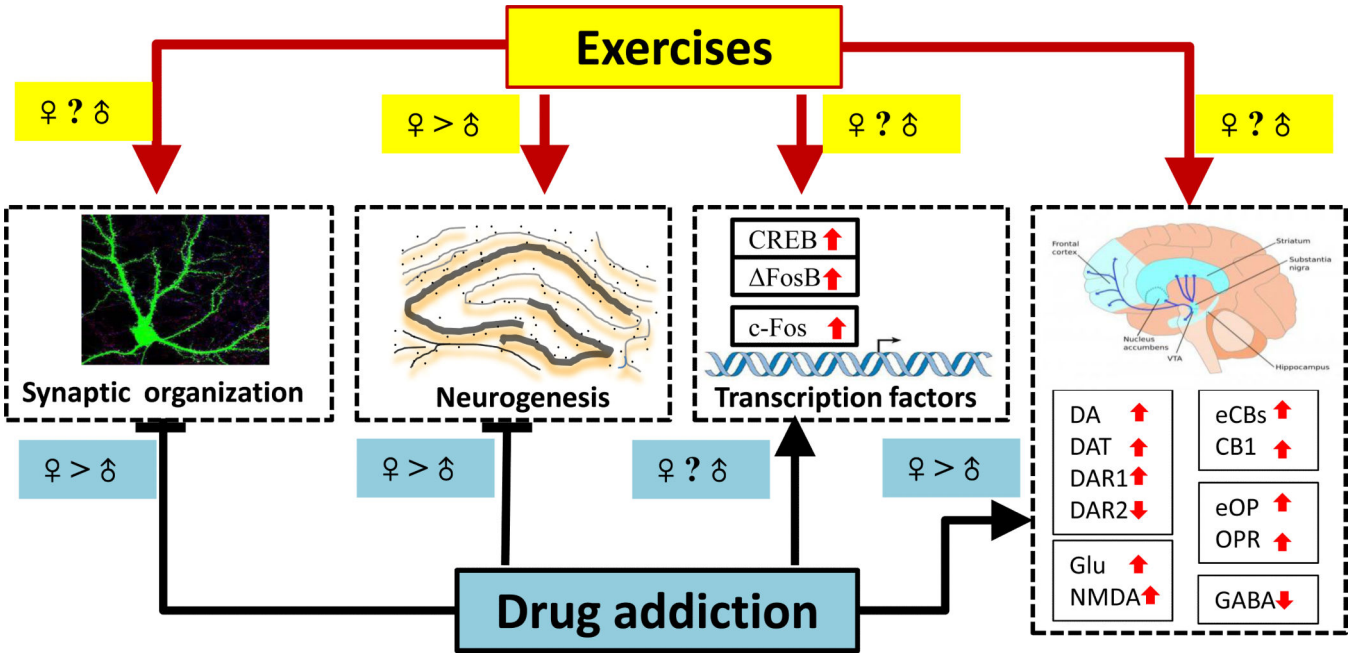

Figure 1. The neurobiology of sex difference in drug addiction and exercise intervention

Drug addiction induces impairment of synaptic organization and neurogenesis, while exercise promotes synaptic plasticity and neurogenesis. In most of reports, males showed greater effect than females. Drug addiction is also altering several transcriptional factors and up-regulating neurotransmitters in specific brain regions, and exercise shared the similar signaling pathways to modulate and normalize the drug addiction related neuropathology. While there are no clear sex difference in exercise-induced regulation of synaptic plasticity and brain neurotransmitters, the sex differences in drug addiction- or exercise-induced alternation of transcriptional factors are brain regional dependent indicated as DA=dopamine; DAT=dopamine transporter; DAR=dopamine receptor; Glu=glutamate; NMDA=glutamate receptor; eCBs=endocannabinoids; CB1= cannabinoid receptor 1; eOP=endogenous opioid; OPR=opioid receptor; GABA=gamma-amino acid.

Table 1

Animal studies for sex differences in effects of exercise on drug addiction (single-sex)

Prevention effect										
						Exercise schedule				
Citation	**Subjects**	**Sex**	**Age /Weight**	**Drug**	**Model**	**Type**	**Duration**	**Frequency**	**Intensity**	**Outcome of exercise**
Lett et al. (2002)	Rats	M	184g	Morphine	CPP	VR	8 days	2-h/day, 1times/day	---	Advantage
Eisenstein et al. (2007)	Rats	M	250-275g	Morphine	CPP	VR	3 weeks	24-h/day	---	Disadvantage
Xu et al. (2007)	Mice	M	3 weeks	Morphine	CPP	VR	2 months	24-h/day	---	Advantage
Chen et al. (2008)	Mice	M	8 weeks	MDMA	CPP	FR	4/8/12weeks	1-h/day,5days/wk	10~12m/min	Advantage
Hosseini et al. (2009)	Rats	M	250-300g	Morphine	SA	FR	11 or 30 days	90 min/day, 1times/day	15m/min	Advantage
EI Rawas et al. (2009)	Mice	M	3 weeks	Heroin	CPP	VR	2 months	24-h/day, 1times/day	---	Advantage
Solinas et al. (2009)	Mice	M	3 weeks	Cocaine	CPP	VR	2~3 months	24-h/day	---	Advantage
Fontes-Ribeiro et al. (2011)	Rats	M	8 weeks	Amphetamine	CPP	FR	8 weeks	50min/day,5days/wk	7~32 m/min	Advantage
Miladi-Gorji et al. (2011)	Rats	M	Adult	Morphine	*	VR	10 days	24-h/day	---	Advantage
Smith and Pitts (2011)	Rats	M	3 weeks	Cocaine	SA	VR	6 weeks	24-h/day	4500m/day	Advantage
Mustroph et al. (2011)	Mice	M	5 weeks	Cocaine	CPP	VR	30 days	24-h/day	8300m/day	Advantage or Disadvantage
O'Dell et al. (2012)	Rats	M	Adult	METH	**	VR	6 weeks	24-h/day	8000m/day	Advantage
Smith and Pitts (2012)	Rats	M	3 weeks	Heroin	SA	VR	6 weeks	24-h/day	4500m/day	Advantage
McCulley et al. (2012)	Rats	M	6 weeks	Alcohol	#	VR	10 days	24-h/day	---	Advantage
Miller et al. (2012)	Rats	M	200-250g	METH	SA	VR	7~14days	1-h/day, 1times/day	---	Advantage or no effect
Hashemi et al. (2013)	Rats	M	220-250g	Alcohol	&&&	FR	2~8 weeks	1-h/day,5days/wk	17 m/min	Advantage
Renteria et al. (2013)	Rats	M	200-250g	Cocaine	*	VR	5~10 weeks	24-h/day	---	Advantage
Engelmann et al. (2014)	Rats	M	200-250g	METH	SA	VR	6 weeks	24-h/day	---	Advantage or Disadvantage
Geuzaine et al. (2014)	Mice	M	4 weeks	Cocaine	CPP	VR	10 weeks	24-h/day	---	Advantage
Smith et al. (2008)	Rats	F	3 weeks	Cocaine	SA	VR	6 weeks	24-h/day	10120 m/day	Advantage
Smith et al. (2008)	Rats	F	3 weeks	Cocaine	CPP	VR	6 weeks	24-h/day	9418 m/day	Disadvantage
Leasure et al. (2010)	Rats	F	190-220g	Alcohol	&	VR	14 days	12-h/day, 1times/day	---	Advantage
Smith and Witte (2012)	Rats	F	3 weeks	Cocaine	SA	VR	6 weeks	24-h/day	7700 m/day	Advantage or no effect
Zlebnik et al. (2014)	Rats	F	90 days	Cocaine	*	VR	21 days	24-h/day	---	Advantage

Table 2

Animal studies for sex differences in effects of exercise on drug addiction (double-sex)

Citation	Subjects	Age	Drug	Model	Exercise schedule				Sex difference	Outcome of exercise
						Duration	Frequency	Intensity		
Prevention effects										
Ehringer et al. (2009)	Mice	Adult	Alcohol	#	VR	13 days	Daily, 24-h/day	---	Yes	Reduced alcohol consummation significantly in females, while no differences were found in males.
Thanos et al. (2010)	Rats	6 weeks	Cocaine	CPP	FR	6 weeks	5 days/week, 1-h/day	10m/min	Yes	Blocked the formation of CPP in males, attenuated the CPP in females.
Smith et al. (2011)	Rats	3 weeks	Cocaine	SA	VR	6 weeks	Daily, 24-h/day	M: 3850m/day F: 9500m/day	No	Weaken SA in both sexes, although the escalating intake was more in females than males.
Smith et al. (2012)	Rats	3 weeks	Cocaine	SA	VR	6 weeks	Daily, 24-h/day	M: 4000m/day F: 8500m/day	No	Decreased reinstatement in both sexes, although females exhibited faster extinction of response than males.
Devaud et al. (2012)	Rats	6 weeks	Alcohol	##	VR	10 days	Daily, 24-h/day	---	No	Attenuated withdrawal-induced increases in seizure susceptibility in male and female rats.
Treatment effects										
Cosgrove et al. (2002)	Rats	Adult	Cocaine	SA	VR	10 days	Daily, 24-h/day	---	Yes	Suppressed SA in females, but not in males.
Brocardo et al. (2012)	Rats	6 weeks	Alcohol	##	VR	10 days	Daily, 24-h/day	M: 2670m/day F: 5380m/day	Yes	Reversed the depressive-like behaviors in males, but not in females.
Sanchez et al. (2014)	Rats	Adolescent	Nicotine	SA	VR	10 days	Daily, 2-h/day	---	Yes	Reduced SA in males, access to a wheel, either locked or unlocked, was sufficient to lower the seeking in females.
Peterson et al. (2014)	Rats	Adult	Cocaine	SA	VR	14 days	Daily, 24-h/day 1,2,6,24-h/day	---	Yes	Male rats were more sensitive than females to exercise-induced attenuation of cocaine-seeking.
Zlebnik et al. (2014)	Rats	Adult	Cocaine	SA	VR	14 days	Daily, 6-h/day	---	Yes	Attenuated extinction responses and cocaine-primed reinstatement in females, but not in males.

#Unlimited access two-bottle choice (water or ethanol) model, and limited access drinking in the dark

##Administrated by a nutritionally complete liquid diet

Table 3

Human studies for sex differences in effects of exercise on drug addiction (single-sex)

Citation	Subjects	Sex	Age (years)	Drug	Exercise schedule				Outcome of exercise
					Type	Duration	Frequency	Intensity	
Prevention effect									
Terry-McEIrath et al.(2011)	HS	M	18-25/26	Alcohol/ Nicotine/ Cannabis	---	---	1-5 days/wk	---	Advantage
Terry-McEIrath et al.(2011)	MS	M	15-18	Alcohol/ Nicotine/ Cannabis	---	---	1-5 days/wk	---	Advantage or disadvantage
Mattila et al.(2012)	Conscripts	M	18-29	Nicotine	---	6 months	> 1 times/wk	Highly/Moderate /Light	Advantage or disadvantage
Henchoz et al.(2014)	Conscripts	M	18-25	Alcohol/ Nicotine/ Cannabis	---	12 months	0-7 days/wk	---	Advantage
Henchoz et al.(2014)	Conscripts	M	18-25	Alcohol/ Nicotine/ Cannabis	---	15 months	0-7 days/wk	---	Advantage or disadvantage
Treatment effect									
Li at al. (2002)	Addicts	M	18-52	Heroin	Qigong	10 days	Daily	---	Advantage
Marcus et al. (1995)	Smokers	F	22-56	Nicotine	Cycle ergometer	15 weeks	3 days/wk	Vigorous	Advantage
Marcus et al. (1999)	Smokers	F	18-65	Nicotine	---	12 weeks	3 days/wk	Vigorous	Advantage
Bock et al. (1999)	Smokers	F	Adults	Nicotine	---	12 weeks	3 days/wk	Vigorous	Advantage
Marcus et al. (2005)	Smokers	F	18-65	Nicotine	Walking, *etc*	8 weeks	5 days/wk	Moderate	Advantage
Prapavessis et al. (2007)	Smokers	F	18-62	Nicotine	Cycle ergometer	12 weeks	3 days/wk	Vigorous	Advantage
Kinnunen et al. (2008)	Smokers	F	18-55	Nicotine	---	19 weeks	2 days/wk	Moderate	Advantage
Vickers et al. (2009)	Smokers	F	18-65	Nicotine	---	10 weeks	5 days/wk	---	Advantage
Bock et al. (2010)	Smokers	F	---	Nicotine	Yoga	8 weeks	2 days/wk	---	Advantage
Williams et al. (2010)	Smokers	F	18~65	Nicotine	Brisk walking	8 weeks	3 days/wk	Moderate	Advantage
Williams et al. (2011)	Smokers	F	18~65	Nicotine	Brisk walking	1 weeks	3 days/wk	Moderate	Advantage
Korhonen et al. (2011)	Smokers	F	18~55	Nicotine	---	15 weeks	---	Moderate	Advantage
Smits et al. (2012)	Smokers	F	Adults	Nicotine	---	15 weeks	3 days/wk	Vigorous	Advantage
Li et al. (2013)	Addicts	F	18-41	Heroin	Tai Chi	6 months	3 days/wk	---	Advantage

HS: high school students; MS: middle school students

Table 4

Human studies for sex differences in effects of exercise on drug addiction (double-sex)

Citation	Subjects(age)	Drug	Exercise schedule				Sex difference	Outcome of exercise
			Type	Duration	Frequency	Intensity		
Prevention effects								
Aaron et al. (1995)	MS	Nicotine/Alcohol	---	---	---	H, L, M	Yes	Less likely to smoke and use alcohol in females and males, respectively
Pate et al. (1996)	HS	Alcohol		2 weeks	2-7 days/wk	L, V	Yes	Less physical activity is associated with higher alcohol use in females, not in males
Pate et al. (2000)	HS	Nicotine/Cocaine/Marijuana	---	12 months	---	L, V	Yes	Exercise reduced usage of illegal drugs in males, not in females
Kulig et al.(2003)	HS	Nicotine/Alcohol/Marijuana	---	---	---	V	Yes	Physical activities reduce use of illicit drugs in females
Moore et al. (2005)	MS	Nicotine/Alcohol/Marijuana	IS	---	---	---	Yes	Reduction or increase in drug use in males and females are sports type dependent
Strohle et al. (2007)	Residents	Nicotine/Alcohol	---	---	1-7 days/wk	---	Yes	Reduced d rates of drugs abuse in females more than males
Korhonen et al.(2009)	Twins	Alcohol/Illicit drugs	---	---	3-7 days/wk	---	Yes	Persistent physical activity decreased illicit drug use more significant in females
Rodriguez et al.	HS	Nicotine	---	---	3-7 days/wk	---	NO	Physical excises significantly reduced tobacco use in both males and females.
Treatment effect								
Chen et al. (2010)		---	Q	14 days	weekly	---	Yes	Females showed more reduced craving, anxiety and withdrawal symptoms than
Horn et al. (2011)		Nicotine	---	10 weeks	1 day/wk	---	Yes	Decreased the risk of continued smoking, particularly for males.
Dolezal et al. (2013)		Methylamphetamine	TE	8 weeks	3 days/wk	M	Yes	Enhanced recovery from drug dependency mainly in men

HS: high school students; MS: middle school students; IS:Individual sports; Q: Qigong; TE:Treadmill exercise; H: High; L:Low; M: Moderate; V: Vigorous