Neuroscience and Biobehavioral Reviews 37 (2013) 1622–1644

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis

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ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form 29 April 2013
Accepted 13 June 2013

Keywords:
Addiction
Animal models
Chromatin
Clinical
Dopamine
Epigenetic
Exercise
Glutamate
Neurobiological mechanisms

ABSTRACT

Physical activity, and specifically exercise, has been suggested as a potential treatment for drug addiction. In this review, we discuss clinical and preclinical evidence for the efficacy of exercise at different phases of the addiction process. Potential neurobiological mechanisms are also discussed focusing on interactions with dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. *While exercise generally produces an efficacious response, certain exercise conditions may be either ineffective or lead to detrimental effects depending on the level/type/timing of exercise exposure, the stage of addiction, the drug involved, and the subject population.* During drug use initiation and withdrawal, its efficacy may be related to its ability to facilitate dopaminergic transmission, and once addiction develops, its efficacy may be related to its ability to normalize glutamatergic and dopaminergic signaling and reverse drug-induced changes in chromatin via epigenetic interactions with brain-derived neurotrophic factor (BDNF) in the reward pathway. We conclude with future directions, including the development of exercise-based interventions alone or as an adjunct to other strategies for treating drug addiction.

Contents

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0149-7634/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2013.06.011

1. Introduction

Drug addiction is the leading cause of preventable death in the United States followed closely by obesity (Mokdad et al., 2004). New and more effective treatments are critically needed, but developing treatments for drug addiction is challenging because its underlying neurobiology varies over time as the disease progresses. During early "non-addicted" stages, such as when drug use is initiated, dopamine signaling in the reward pathway (i.e., nucleus accumbens, NAc; ventral tegmental area, prefrontal cortex, PFC) is believed to be a primary mechanism motivating drug use (for reviews see Gardner, 2011; Kalivas and Volkow, 2005; Koob and Volkow, 2010; Pierce and Kumaresan, 2006; Willuhn et al., 2010). Drugs of abuse, including psychostimulants, alcohol, nicotine, hallucinogens, cannabinoids, and opiates increase dopamine in the NAc (Carboni et al., 1989; Chen et al., 1990; Damsma et al., 1989; Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988; Maisonneuve et al., 1991; Yoshimoto et al., 1992). Blocking/ablating this pathway can disrupt drug self-administration, particularly psychostimulant self-administration (e.g., Chang et al., 1994; Corrigall et al., 1992; Lyness et al., 1979; Singer et al., 1982; Singer and Wallace, 1984; Robledo et al., 1992; but see Lyness and Smith, 1992 for ethanol self-administration and Gerrits and Van Ree, 1996 for heroin self-administration). Other signaling pathways, such as glutamatergic pathways, also motivate drug use, particularly during later stages of the addiction process (i.e., with recurrent use, once addiction has developed, during relapse; e.g., Allen et al., 2007; Bauer et al., 2013; Ben-Shahar et al., 2009, 2012, 2013; Bossert et al., 2012; Fischer-Smith et al., 2012; Ghasemzadeh et al., 2011; Hao et al., 2010; Kufahl et al., 2011, 2013; Madayag et al., 2007; McCutcheon et al., 2011; Meinhardt et al., 2013; Okvist et al., 2011; Schwendt et al., 2012; Sidhpura et al., 2010; for reviews see Kalivas and Volkow, 2011; Loweth et al., 2013; Van den Oever et al., 2012; Wolf and Tseng, 2012). Brain adaptations caused by chronic exposure to drugs of abuse also leads to mesolimbic hypofunction (Koeltzow and White, 2003; Maisonneuve et al., 1995; Paulson et al., 1991; Schmidt et al., 1996), which in turn, may promote drug use to compensate for its decreased effect on dopamine release and may motivate relapse to drug use during abstinence to reverse dopamine deficits (for review see Melis et al., 2005). Chronic exposure to drugs of abuse also leads to alterations in gene expression through neuronal chromatin remodeling (e.g., Damez-Werno et al., 2012; Gozen et al., 2013; Repunte-Canonigo et al., 2013; Tomasiewicz et al., 2012), and these changes may underlie the persistent vulnerability to relapse after extended periods of abstinence (for reviews see Biliński et al., 2012; Kovatsi et al., 2011; LaPlant and Nestler, 2011; Robison and Nestler, 2011). Together, these results suggest that the efficacy of a potential treatment for drug addiction should be tailored for the stage of the addiction process. This type of approach has been used successfully in the treatment of other diseases (e.g., diabetes, cancer, HIV), but has not been fully considered for addiction treatment.

Physical activity, and specifically exercise, is a potential non-pharmacological treatment for addiction that targets systems implicated in both early and late stages of the addiction process and has secondary health benefits (e.g., prevention of obesity and secondary diseases such as diabetes). Mechanistically, physical activity and exercise activate the same reward pathway as drugs of abuse, through increases in dopamine concentrations and dopamine receptor binding (Greenwood et al., 2011; MacRae et al., 1987). These effects may be particularly beneficial at preventing drug use and reducing initial vulnerability to drug use. Physical activity and exercise also decrease glutamate in the striatum (Guezennec et al., 1998), which may protect against overstimulation of glutamatergic receptors following chronic drug exposure. Exercise may also influence brain plasticity through mechanisms centered on remodeling of chromatin at regions that are implicated in drug addiction (Gomez-Pinilla et al., 2011; Chase and Sharma, 2013; Kumar et al., 2005; Sadri-Vakili et al., 2010; Vassoler et al., 2013; Wan et al., 2011).

Despite promising results, certain exercise conditions may be either ineffective or lead to detrimental effects. Given that exercise is becoming more frequently considered as a potential treatment for addiction and other psychiatric disorders, and given that it is a relatively easily implemented and freely available option, it is critical to identify the conditions that produce beneficial effects, and those that may lead to detrimental effects. In this review, we will discuss evidence for the efficacy of physical activity and exercise at reducing drug use at the different stages of the addiction process including the initiation of use, the transition to addiction, withdrawal, and relapse. Although the main goal is to understand the potential efficacy of exercise as a treatment for addiction, evidence for the effects of both physical activity and exercise are discussed. "Physical activity" is used to describe findings primary from epidemiological studies that are generally self-reported levels of daily activities, including occupational, sports, conditioning, household, or other activities. "Exercise" is used to describe findings primary from the human laboratory and some epidemiological studies, and refers to a subset of physical activity that is structured and repetitive (e.g., treadmill running, walking). *Studies were selected based on Pub Med and Web of Science searches using the key words exercise, physical activity, smoking, nicotine, tobacco, heroin, morphine, opioid, cocaine, methamphetamine, illicit drug use/abuse/dependence, marijuana, and alcohol. In cases where meta-analytical studies were available, these reviews were preferentially discussed over the individual studies.* We also reviewed findings from animal models of exercise, including both forced and voluntary running on a treadmill or a wheel, in order to identify potential mechanisms for its efficacy. To this end, we focused on three signaling pathways/mechanisms critically involved in the development and maintenance of addiction: dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. The potential role of other signaling pathways, including the endogenous opioid pathway, is also briefly discussed. *In addition to the key words used to identify human studies, we included the terms wheel and treadmill running, as well as dopamine, glutamate, chromatin, epigenetic, and Bdnf.* We conclude with future directions including the potential role of exercise as an intervention for drug addiction.

2. Effects of exercise on initiation of drug use

2.1. Initiation of drug use: Results from human studies

In humans, the initiation phase encompasses the transition from initial drug sampling to regular use. Although a causal effect of exercise on rates of initiation of drug use in humans has not been examined, epidemiological data obtained from adolescents, a population believed to be particularly vulnerable to initiate drug use, indicate a negative association of the two. For example, results from school-based, community-based, and national cross-sectional studies show that that highly active teens, teens who exercise regularly, and teens involved in team sports are less likely than less active teens, teens who do not exercise, and teens not involved in team sports to use cigarettes and illicit drugs (e.g., Escobedo et al., 1993; Field et al., 2001; Kirkcaldy et al., 2002; Kulig et al., 2003; Martinsen and Sundgot-Borgen, 2012; Melnick et al., 1997; Pastor et al., 2003; Pate et al., 1996, 2000; Rainey et al., 1996; Ströhle et al., 2007; Terry-McElrath et al., 2011; See Table 1 for representative summary of the studies and findings). Results from longitudinal studies reveal similar findings where high levels of physical activity