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Review

Does physical activity protect against drug abuse vulnerability?

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ABSTRACT

Background: The current review examined recent literature to determine our state of knowledge about the potential ability of physical activity serve as a protectant against drug abuse vulnerability.
Methods: Both preclinical and clinical studies were examined using either associational or random assignment study designs. In addition to examining drug use as an outcome variable, the potential neural mediators linking physical activity and drug abuse vulnerability were examined.
Conclusions: Several important conclusions may be drawn. First, the preclinical evidence is solid in showing that physical activity in various forms is able to serve as both a preventive and treatment intervention that reduces drug use, although voluntary alcohol drinking appears to be an exception to this conclusion. Second, the clinical evidence provides some evidence, albeit mixed, to suggest a beneficial effect of physical activity on tobacco dependent individuals. In contrast, there exists only circumstantial evidence that physical activity may reduce use of drugs other than nicotine, and there is essentially no solid information from random control studies to know if physical activity may prevent initiation of problem use. Finally, both preclinical and clinical evidence shows that various brain systems are altered by physical activity, with the medial prefrontal cortex (mPFC) serving as one potential node that may mediate the putative link between physical activity and drug abuse vulnerability. It is concluded that novel neurobehavioral approaches taking advantage of novel techniques for assessing the physiological impact of physical activity are needed and can be used to inform the longitudinal random control studies that will answer definitively the question posed.

Contents

1. Introduction

There is a widespread recognition that physical activity and voluntary exercise are important components of a healthy lifestyle. During early stages of life, physical activity enhances social development and learning (Parcel et al., 1989), whereas later in life, it can help slow the physical and cognitive decline associated with aging (Cotman and Berchtold, 2007). In addition, physical activity is useful in the prevention and treatment of various disease states, including Alzheimer's disease (Cotman and Berchtold, 2007), obesity-related metabolic diseases (Bensimhon et al., 2006; Brown and Summerbell, 2009; Qin et al., 2010), and psychiatric disorders

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such as anxiety, depression and schizophrenia (Brown et al., 2013; Holley et al., 2011; Strohle, 2009). The beneficial effects of physical activity on health-related outcomes are thought to be mediated by a wide range of long-term biological alterations, which likely explain the multiple benefits across various disease states. For example, exercise reduces the incidence of obesity-related diseases, at least in part, by altered lipoprotein levels (Ainslie et al., 2005; Craig et al., 1996). In contrast, the ability of physical activity to enhance learning during development may be mediated by the proliferation of glial and endothelial cells, as well as an increases in neurogenesis and neuronal connectivity, in brain regions critical for learning and memory (Eckert and Abraham, 2013; Gelfo et al., 2009; Mandyam et al., 2007; Viola et al., 2009).

Given the widespread benefits with various disease states, there has been a recent initiative to determine whether physical activity and exercise have utility in the prevention and treatment of substance use disorders. In 2008, the National Institute on Drug Abuse convened a meeting in Bethesda, Maryland around the topic entitled "Can Physical Activity and Exercise Prevent Drug Abuse"? Shortly afterwards, a Request for Applications (RFA) was issued targeting this important area of investigation. More recently, a funding opportunity announcement (FOA) subsequently was released in August, 2014 by the NIH Office of Disease Prevention entitled "Developing and Testing Interventions for Health-Promoting Physical Activity" to help address this continuing challenge, with the goal of achieving the 2008 Physical Activity Guidelines for Americans (www.health.gov/paguidelines/guidelines/default.aspx).

While some success has been achieved in our understanding of the influence of physical activity on drug abuse prevention and treatment (Linke and Ussher, 2015; Lynch et al., 2013; Smith and Lynch, 2011), notable gaps persist. In particular, there is little information about the neurobiological mechanisms that specifically mediate the relation between physical activity and drug abuse vulnerability in humans. Further, while exercise-induced changes in reward-relevant neural systems are likely important (Lynch et al., 2013), there has been little consideration of other neurobehavioral processes such as impulsivity, stress, executive cognitive function, and emotion regulation.

In the current review, we update the major preclinical and clinical findings that have emanated since the NIDA meeting in 2008. In the case of preclinical research, a brief summary of key neural mechanisms thought to mediate the effects of physical activity and enrichment on drug reward are presented. While physical activity produces global changes throughout the brain, the medial prefrontal cortex (mPFC) may play a pivotal role in the relation between physical activity and drug abuse vulnerability. The mPFC is known to have a role in various addiction-related processes, including reward sensitivity, inhibitory control, stress reactivity and emotion regulation (Koob et al., 2014; Perry et al., 2011; Rive et al., 2013). Further, the current review highlights a few recent reports that illustrate the effectiveness of physical activity in preventing and treating drug use/abuse. However, some significant barriers have impeded translation of preclinical neurobiological evidence to humans. Recommendations for further research to address this important issue are offered.

2. Does physical activity protect against drug abuse?

Although there has been some success in developing school-, family- and media-based preventive interventions to reduce drug abuse risk among at-risk adolescents (Griffin and Botvin, 2010; Hansen, 2010; Palmgreen and Donohew, 2010), these interventions are not fully or widely effective across a range of individuals. Similarly, for treatment interventions among individuals with substance use disorders, novel medications and immunotherapies for the treatment of substance use disorders have been pursued (Koob et al., 2009; Montoya and Vocci, 2008; Shen and Kosten, 2011), but these medical treatments are not effective across a wide range of individuals and side effect profiles are sometimes problematic. As discussed below, both preclinical and clinical results are now beginning to provide evidence that an effective alternative approach is to implement intervention strategies that promote physical activity. This may be accomplished by evaluating physical activity alone or in combination with other preventive and/or treatment modalities.

2.1. Preclinical evidence

At the preclinical level, there is considerable overlap in the protective effects of either physical activity or environmental enrichment on drug use, most likely because exposing animals to enriching stimulation elevates levels of physical activity and reduces body weight (Bardo and Hammer, 1991; Diamond et al., 1965). For the purpose of this review, however, we focus on physical activity separately, as enrichment in the absence of physical activity may not induce all of the neurogenic factors responsible for activity-dependent brain adaptations (Kobilo et al., 2011).

A host of neural, social and individual difference factors are known to play a role in drug taking behavior. Regardless of the mechanism, however, a consistent finding among preclinical studies is that physical activity reduces drug self-administration. This basic finding has been reported across various laboratories and methodologies, as well as across different developmental periods (adolescent and adult) and across both sexes (see Table 1); however, some sex differences exist in the literature, as described previously (Lynch et al., 2013). In both rats and mice, the most common method for promoting physical activity is to provide access to a running wheel, although a treadmill or swimming regimen also have been used. The beneficial effect of physical activity is most notable when access to a running wheel occurs during the self-administration session (Cosgrove et al., 2002; Kanarek et al., 1995; Zlebnik et al., 2012). However, when access to a running wheel is implemented either before or after daily operant conditioning sessions, a decrease in intravenous self-administration also is obtained across different various drugs, including cocaine (Smith et al., 2008b; Smith et al., 2011), methamphetamine (Engelmann et al., 2013; Miller et al., 2012), heroin (Smith and Pitts, 2012) and morphine (Hosseini et al., 2009). Physical activity also decreases the escalation of self-administration (Engelmann et al., 2013; Zlebnik et al., 2012) and reinstatement (Lynch et al., 2010; Sanchez et al., 2013; Smith et al., 2012; Thanos et al., 2013; Zlebnik et al., 2010). Especially relevant to human tobacco cessation treatments, physical activity also decreases reinstatement of nicotine seeking following a period of extinction (Sanchez et al., 2013). Thus, regardless whether applied concomitantly or non-concomitantly with access to drug, engagement in physical activity has a protective effect across different stages of the addiction cycle.

Since wheel running alone is rewarding (Rasmussen and Hillman, 2011; Silva and Heyman, 2001; Trost and Hauber, 2014), one potential explanation for the decrease in self-administration is that access to a running wheel serves as an alternative non-drug reinforcer. Based on principles of behavioral economics, physical activity can be viewed as a non-drug substitute that interacts with the unit price of a drug, similar to how responding for drug reward will decrease in humans when a monetary reward is made available concurrently (Johnson et al., 2004). In rats, food and sweetened solutions are alternative commodities that can decrease demand for a drug (Comer et al., 1996), although these non-drug commodities may enhance elasticity of the demand curve only in highly addicted animals; i.e., the addicted animal is less likely to defend consumption as unit price increases (Lenoir and Ahmed, 2008). Further, when a substitution relationship exists, increasing the value