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Treadmill exercise improves fitness and reduces craving and use of cocaine in individuals with concurrent cocaine and tobacco-use disorder

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ABSTRACT

Exercise may be a useful treatment for substance use disorders. Participants (N=24) included treatment-seeking individuals with concurrent cocaine and tobacco-use disorder (cigarette smokers). Participants were randomized to either running or walking (30 min per session, 3 times per week) or sitting (control condition) for 4 consecutive weeks. Several metrics indicated significant differences among runners, walkers, and sitters during sessions, including mean distance covered and calories burned. In addition, remote physiological monitoring showed that the groups differed significantly according to mean maximum heart rate (HR), respiration, and locomotor activity. Across the 4-week study, exercise improved fitness measures including significantly decreasing resting HR. Though not statistically significant, exercise improved abstinence from cocaine and increased self-reports of no cocaine use in last 24 h. In general, reductions in tobacco use and craving were not as robust. To our knowledge, this is the first study to evaluate the effects of a multi-week exercise program in individuals with concurrent cocaine and tobacco-use disorder. The data clearly show significant improvements in basic fitness measures and several indices reveal that exercise improved both self-report and biochemically verified reports of cocaine abstinence. Taken together, the data from this study provide preliminary evidence for the efficacy of exercise for improving fitness and reducing cocaine use.

1. Introduction

According to the 2013 National Survey on Drug Use and Health, 20.1% of past month cigarette smokers reported current use of an illicit drug compared with 4.1% of persons who were not current cigarette smokers. Cigarette smoking is ~3 times more prevalent in cocaine abusers than in the general population (Brewer et al., 2013; Budney et al., 1993) and cocaine-dependent individuals who are cigarette smokers report using cocaine more frequently and in greater amounts than those who are non-smokers (Roll et al., 1996).

The problems of cocaine and tobacco use disorders remain as major medical and social concerns, and there is a pressing need for a broadly effective treatment approach. While there are several FDA-approved medications for tobacco use disorder (e.g., varenicline), there has not been a single medication identified that reliably reduces cocaine use (Haile et al., 2012). Behavioral interventions, including contingency management (CM) and cognitive behavioral therapy (CBT), are of particular interest as treatments for cocaine use disorder. A systematic evaluation of 19 studies with a total of 1664 patients showed that CM in combination with standard CBT or other psychological interventions increases cocaine abstinence, improves treatment retention, and may also enhance effects produced by medications (Schierenberg et al., 2012). These promising outcomes indicate that non-pharmacological treatment approaches warrant additional consideration. Among available alternatives, a recent review highlighted data showing that physical activity protects against drug abuse vulnerability (Bardo and Compton, 2015), and exercise has been shown to be reinforcing in humans and rodents and may, therefore, be useful as a treatment for substance use disorders (Lynch et al., 2013). A number of other factors enhance the value of exercise-based behavioral interventions, including that they are relatively low cost and easy to implement in comparison to

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medication studies. Furthermore, these types of interventions likely confer additional benefits to study participants, including improved cardiovascular function and improved mood.

Individual exercise sessions have been shown to attenuate cravings and withdrawal symptoms in cigarette smokers (Janse Van Rensburg et al., 2009; Kurti and Dallery, 2014; Taylor et al., 2007). However, exercise trials lasting several weeks have not consistently shown reductions in craving or improvements in abstinence from cigarette smoking (Abrantes et al., 2014). In a recent meta-analytic review of exercise interventions for smoking, the authors recommended trials with sufficiently intense interventions, equal contact control conditions, and measures of exercise adherence and change in physical activity in both exercise and comparison groups (Ussher et al., 2012).

Several reports have recently emerged evaluating the effects of exercise interventions on methamphetamine use. In one key study, an 8-week exercise intervention was utilized and the data showed that lower severity users ($\leq$ 18 days/month) exhibited reductions in methamphetamine use at three time-points after study completion (Rawson et al., 2015). In a separate study, stationary cycling was also shown to reduce craving and inhibitory deficits in methamphetamine users (Wang et al., 2015). Last, exercise training (3 times weekly for 8 weeks) significantly increased striatal dopamine (DA) D_2/D_3 binding potential in methamphetamine users (Robertson et al., 2016), which is likely of considerable import given that long-term methamphetamine use has been previously shown to reduce striatal DA binding (Volkow et al., 2001). Taken together, available data suggest that exercise may reduce methamphetamine use and change brain DA systems.

Importantly, the effects of exercise on cocaine use or craving have not been investigated in humans. However, several reports in rodents show that exercise (i.e., wheel running) reduced cocaine self-administration (Cosgrove et al., 2002; Smith et al., 2008; Zlebnik and Carroll, 2015) and reinstatement of cocaine seeking (Lynch et al., 2010; Ogbonmwan et al., 2015; Thanos et al., 2013). Importantly, rats exposed to 8-weeks running on a treadmill with increasing intensity exhibited reductions in amphetamine-induced DA release (Marques et al., 2008), indicating a potential mechanism of action for this type of intervention.

For this study, we sought to establish for the first time the effects of treadmill exercise on basic fitness measures and objective and subjective measures of cocaine and tobacco use and craving in human volunteers.

2. Methods

The current study was approved by the Baylor College of Medicine institutional review board and the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) Research & Development Committee. Participants were recruited from the Houston area primarily using fliers and newspaper advertisements. Key inclusion criteria were that volunteers be between 21 and 55 years of age, meet DSM criteria for concurrent cocaine- and tobacco-use (cigarette smokers) disorder, be seeking treatment for cocaine use disorder, and have a medical history and brief physical examination demonstrating no clinically significant contraindications for participation in a rigorous exercise program. Participants read and confirmed understanding of the informed consent and were compensated for their time at the conclusion of each week of the study.

Using a between subjects study design, participants were randomized to either running (N=10), walking (N=7) or sitting (N=7; control condition) 3 times per week (30 min per session) for 4 consecutive weeks. The control condition involved sitting passively (for the same period of time) in the laboratory without access to reading materials, mobile phone, or internet, and was based on that used in previous exercise studies in cigarette smokers (Janse Van Rensburg et al., 2009). The 4-week duration of the protocol was chosen for two key reasons. First, this study was designed to mimic the duration and frequency of visits of another protocol completed using this population of individuals (cocaine-dependent smokers) in our lab (Yoon et al., 2013). Second, this protocol was designed with this specific cohort in mind assuming that few of the individuals recruited might be willing to participate in a longer, multi-week (8- or 12-weeks) exercise study (which is a duration commonly used in healthy, non-drug using participants). Distinct groups for runners and walkers were included in this study (rather than just a single moderate intensity "exercise" group) to facilitate an examination of dose response effects of exercise on fitness variables, as well as cocaine- and tobacco-use outcomes.

Participants were not required, nor instructed, to refrain from either tobacco or cocaine use prior to attending any study session. Recent tobacco use was confirmed via breath carbon monoxide (CO) and recent cocaine use was evaluated using a urine toxicology screen (described below). It is important to mention that no participant exhibited signs of acute cocaine intoxication, even those who tested positive for cocaine metabolites in their urine, at the start of any exercise session.

2.1. Bioharness

Remote physiological monitoring of heart rate (HR), respiration, and locomotor activity was accomplished using Bioharness (Zephyr, Annapolis, MD). The validity and reliability of Bioharness measures has been evaluated under controlled laboratory conditions and field-based assessments (Johnstone et al., 2012a, 2012b, 2012c). More recently, studies have begun to examine the clinical and research utility of Bioharness in hospital and exercise settings (Bianchi et al., 2013; Brooks et al., 2013; Kim et al., 2013), and our lab recently demonstrated the usefulness of this device to monitor discreet changes in HR, respiration and body temperature in individuals exposed to an acute dose of cocaine in the laboratory (Yoon et al., 2014). In the current study, Bioharness devices were worn by participants throughout study visits (including specifically throughout the exercise session) so that accurate and detailed exercise profiles could be established.

2.2. Treadmill test

A treadmill test was conducted during screening based on the standard, graded Balke-Ware protocol as described in the 2006 American College of Sports Medicine guidelines. The treadmill test was used primarily for determining maximum and target HR (described in next section) for individuals who were deemed eligible for study enrollment. After resting blood pressure and HR were recorded, participants started walking at a treadmill speed of 2 mph at 0% elevation for 1 min. Treadmill speed was increased 0.5 mph/min with no increase in elevation until treadmill speed was set at 3 mph. After 1 min at speed of 3 mph and 0% elevation, treadmill speed was set at 3.3 mph with 1% elevation. Speed was maintained at 3.3 mph and elevation increased by 1% per minute. Testing was terminated when the participant reached volitional fatigue and could not maintain the pace any longer, or any time the participant expressed desire to stop. After reaching the test termination point the treadmill speed was set back to 2 mph at 0% elevation for a minimum of 3 min for the cool down stage. HR was monitored continuously throughout this session using Bioharness.