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Exercise as a potential treatment for drug abuse: evidence from preclinical studies

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Epidemiological studies reveal that individuals who engage in regular aerobic exercise are less likely to use and abuse illicit drugs. Until recently, very few studies had examined the causal influences that mediate this relationship, and it was not clear whether exercise was effective at reducing substance use and abuse. In the past few years, several preclinical studies have revealed that exercise reduces drug self-administration in laboratory animals. These studies have revealed that exercise produces protective effects in procedures designed to model different transitional phases that occur during the development of, and recover from, a substance use disorder (e.g., acquisition, maintenance, escalation, and relapse/reinstatement of drug use). Moreover, recent studies have revealed several behavioral and neurobiological consequences of exercise that may be responsible for its protective effects in these assays. Collectively, these studies have provided convincing evidence to support the development of exercise-based interventions to reduce compulsive patterns of drug intake in clinical and at-risk populations.

Keywords: aerobic exercise, drug-seeking behavior, drug self-administration, physical activity

Epidemiological studies consistently report that aerobic exercise is inversely related to substance use and abuse. The inverse relationship between aerobic exercise and substance use may be attributed to three possible factors. First, exercise could lead to a causal decrease in substance use, either by serving as an alternative, non-drug reinforcer, or by producing functional neuroadaptations that influence an individual's susceptibility to developing a substance use disorder. Second, substance use could lead to a causal decrease in exercise, either by reducing discretionary time/income that would otherwise be spent on recreational activities or by decreasing aerobic capacity to limit an individual's ability to engage in exercise. Third, an external factor could have a causal impact on both activities, such as an underlying personality trait or an influence from the individual's home environment. These three possibilities are not mutually exclusive of one another, but only the first possibility provides a theoretical framework from which to design exercise-based interventions to decrease substance use and abuse. Clinical studies, with proper control groups, will ultimately be needed to determine whether an exercise-based intervention decreases the likelihood of developing a substance use disorder or reduces relapse in treatment-seeking individuals. To date, few clinical studies have been published in which aerobic exercise was employed as an experimental manipulation and measures of substance use, particularly illicit substance use, was used as a dependent measure. The reasons for the lack of studies are undoubtedly due to the time and monetary expense involved in clinical research, but studies in this area are underway and more are expected. In the meantime, preclinical research will be necessary to determine the causal effects of aerobic exercise on drug self-administration, and to identify the important parameters that influence this relationship.

SIMILARITIES BETWEEN DRUGS AND EXERCISE IN PRECLINICAL MODELS OF REWARD AND REINFORCEMENT

Although most individuals experiment with drugs at some point in their lives, only a minority of individuals use drugs in a manner that meets the clinical definition of abuse. Individuals differ markedly in self-reported drug effects, and a drug may produce positive affective states in some individuals but negative affective states in other individuals (Volkow et al., 1999, 2002). These affective states depend on the dose of the drug and the context in which it is administered, which in turn determines the likelihood of whether it will be self-administered (Volkow and Swanson, 2003). Similar to individual patterns of drug self-administration, all individuals engage in some level of physical activity, but only a minority of individuals engages in an amount that meets the level recommended by public health organizations (Pleis et al., 2010). Similar to drugs of abuse, exercise produces positive affective states in some individuals but negative affective states in others (Ekkekakis et al., 2010), and these affective states depend on the intensity of exercise and the situational context (Ekkekakis and Lind, 2006; Ekkekakis et al., 2008; Lind et al., 2008). The one critical difference between the two behaviors is that regular engagement in one is detrimental to health, whereas regular engagement in the other is clearly beneficial.

Under some conditions, exercise increases measures of euphoria and well-being in human populations in a manner similar to that of abused drugs (e.g., Janal et al., 1984; Nabetani and Tokunaga, 2001). In laboratory animals, the positive affective states of exercise are typically examined in the conditioned place preference procedure, an assay in which a stimulus (e.g., an interoceptive state produced by a drug or physical activity) is repeatedly paired with a

distinct environment. If the animal later expresses a preference for the paired environment over a control environment, then one may assume that the experimental manipulation produced a positive affective state in that animal. This procedure has long been used in substance abuse research, and drugs with high abuse liability reliably produce a conditioned place preference under a wide range of conditions (see reviews by Bardo and Bevins, 2000; Tzschentke, 2007). Similarly, pairing a distinctive environment with the after-effects of running produces a conditioned place preference (Lett et al., 2000, 2001; Belke and Wagner, 2005; Greenwood et al., 2011), suggesting that the positive affective states of exercise last beyond the duration of physical activity.

Exercise also functions as a positive reinforcer in laboratory animals, in that animals will perform an operant response (e.g., press a lever) in order to engage in exercise. This effect has been demonstrated in multiple studies employing a variety of experimental parameters (Iversen, 1993; Belke, 1997, 2000; Belke and Dunbar, 2001), and is supported by the observation that laboratory rats, the most common species examined in these studies, will spontaneously run upward of 10 km per day without external inducement (Smith et al., 2011a,b). Exercise also serves as positive reinforcer in humans under some conditions, and like laboratory animals, clinical populations will perform an operant response to engage in aerobic activity (Schebendach et al., 2007).

Many abused substances serve as positive reinforcers in both humans and animals. The drug self-administration procedure is the primary means by which the reinforcing effects of drugs are examined in the laboratory. As a preclinical model, it is often considered the gold-standard by which the motivation to obtain a drug is compared across subject populations and experimental conditions. In the drug self-administration procedure, drug administration is contingent on an operant response (e.g., pressing a lever). A drug is said to serve as a positive reinforcer if the drug maintains responding to a greater degree than that maintained by the drug's vehicle (e.g., saline). The drug self-administration procedure has good face and predictive validity, and drugs that are self-administered by animals tend to be abused by human populations (see reviews by O'Brien and Gardner, 2005; O'Connor et al., 2011). Furthermore, interventions that reduce drug self-administration in the laboratory often reduce drug intake in substance-abusing individuals (see reviews by Mello and Negus, 1996; Haney and Spealman, 2008).

THE EFFECTS OF EXERCISE ON DRUG SELF-ADMINISTRATION: COCAINE, AMPHETAMINE, AND METHAMPHETAMINE

Using the drug self-administration procedure, experimental parameters can be manipulated to model the different transitional phases of substance use and abuse (e.g., acquisition, maintenance, escalation, binge, and relapse/reinstatement). These models of addictive behavior provide a platform by which researchers can critically evaluate interventions that prevent, reduce, or eliminate problematic forms of drug use during different transitional stages of a substance use disorder. Recent studies report that exercise reduces drug self-administration during several of these stages. A number of drugs have been examined in these studies, but cocaine and amphetamine-like drugs have received the most attention.

ACQUISITION

A rapid transition from initial drug experimentation to regular patterns of drug use is viewed as one of the leading prognosticators of whether an individual will later develop problems with substance abuse and dependence. Consequently, one of the goals of primary prevention programs is to discourage the development of regular patterns of drug use in at-risk populations. The acquisition of regular patterns of drug intake after initial drug exposure can be modeled in the laboratory by exposing an animal to non-contingent drug infusions and then permitting the animal to self-administer that drug in free-operant test sessions. Most studies using exercise as an experimental manipulation failed to report differences in the rate of acquisition between sedentary and exercising animals (Smith et al., 2008, 2011a,b; Zlebnik et al., 2010); however, those studies used protocols designed to maximize the rate of acquisition and minimize any differences between groups (e.g., use of a high training dose, prior lever-press training with food reinforcement, baiting the response lever). Only one study used the rate of acquisition as its primary dependent measure, and that study reported significant differences between sedentary and exercising subjects. Smith and Pitts (2011b) examined the effects of voluntary wheel running on the acquisition of cocaine self-administration in experimentally naive rats. Male rats were obtained at weaning and assigned to sedentary or exercising conditions immediately upon arrival. After 6 weeks, rats were surgically implanted with intravenous catheters and placed in operant conditioning chambers for 2 h/day for 15 consecutive days. With the exception of the daily test sessions, exercising rats had free access to their running wheels for the duration of the study. Each session began with a non-contingent priming infusion of cocaine, followed by a free-operant period in which each response on the active lever produced an infusion of cocaine. Compared to sedentary rats, exercising rats acquired cocaine self-administration at a significantly slower rate and emitted significantly fewer active lever presses during the 15 days of behavioral testing. These effects could not be attributed to non-specific differences in rates of operant responding, because the number of responses on an inactive lever did not differ between the two groups. These data suggest that aerobic exercise inhibits the acquisition of cocaine self-administration and may prevent the establishment of regular patterns of substance use in at-risk populations.

MAINTENANCE

The effects of exercise on stable patterns of drug intake during the maintenance phase of drug self-administration have been studied by multiple investigators. At least three studies have shown that drug self-administration is reduced when exercise is available as an alternative non-drug reinforcer. In one of the first studies to demonstrate this effect, Kanarek et al. (1995) reported that concurrent access to a running wheel decreased the oral consumption of a liquid amphetamine solution. This effect was specific to the amphetamine stimulus because consumption of ordinary tap water was unaffected. Similarly, Cosgrove et al. (2002) reported that concurrent access to a running wheel decreased intravenous cocaine self-administration; however, this effect was only statistically significant in females. In that study, the relationship between exercise and cocaine self-administration was reciprocal, in that

concurrent access to cocaine also decreased wheel running, and this effect was observed in both males and females. Consistent with those findings, Miller et al. (2011) reported that concurrent access to a running wheel decreased responding maintained by methamphetamine, provided that the wheel was concurrently available at the outset of self-administration training. Using a slightly different experimental design, Smith et al. (2008) reported that aerobic exercise reduced cocaine self-administration even when a running wheel was not concurrently available during the test sessions. In that study, female rats were obtained at weaning and assigned to sedentary or exercising conditions upon arrival. Six weeks later, rats were implanted with intravenous catheters and trained to self-administer cocaine under positive reinforcement contingencies. Rats with running wheels in their home cages obtained fewer infusions than sedentary rats, and this effect was apparent at both low and high doses of cocaine. In exercising rats, greater exercise output prior to catheter implantation was associated with lower cocaine intake at the high dose of cocaine. These findings suggest that exercise may have protective effects on cocaine self-administration that extend beyond a particular bout of exercise, and that greater degrees of exercise may confer greater degrees of protection.

ESCALATION

Preclinical studies examining the maintenance of drug self-administration achieve very stable levels of drug intake for weeks or months by limiting daily test sessions to 1–2 h in duration. This pattern of drug intake contrasts with that typically observed in substance-abusing populations, who tend to exhibit a progressive escalation of their drug use over time (Gawin, 1991). Such increases in drug intake are a cardinal feature of substance abuse, and comprise a critical component of the diagnostic criteria for substance use disorders by professional organizations. If access to a drug is extended by increasing the duration of daily self-administration sessions, animals exhibit a progressive increase in drug intake that is similar to the escalation of drug use frequently observed in substance-abusing populations. For instance, animals given 6-h access to cocaine in daily self-administration sessions escalate their drug intake over a period of several days, whereas control animals given 1-h daily access exhibit stable patterns of intake over the same period of time (Ahmed and Koob, 1998). In a recent study, Smith et al. (2011b) reported that voluntary wheel running decreased the escalation of cocaine intake under extended-access conditions. In that study, male and female rats were obtained at weaning, housed in either sedentary or exercising conditions for 6 weeks, implanted with intravenous catheters, and trained to self-administer cocaine under positive reinforcement contingencies. Once cocaine self-administration was acquired, sessions were extended to 6 h and the escalation of cocaine intake was examined over 14 consecutive days. Rats in the exercising group had access to their running wheels in their home cages for the duration of the study. Both groups exhibited increases in cocaine intake during the extended-access phase of the study, but this effect was significantly attenuated in the exercising rats. Although females escalated their cocaine intake to a greater extent than males, exercise was effective at attenuating the escalation of cocaine intake in both sexes. These data indicate that aerobic exercise may attenuate the escalation of cocaine intake under extended-access conditions and suggest that exercise may be an effective intervention in preventing escalating patterns of substance use in experienced drug users.

BINGE AND COMPULSIVE USE

One feature of substance use disorders that is particularly problematic from a public health standpoint involves episodes of brief but excessive drug intake, during which an individual exhibits highly dysregulated and compulsive patterns of drug use. These "binges" of excessive drug intake are associated with a number of negative outcomes, including involvement in criminal activity, visits to hospital emergency departments, and participation in high-risk sexual encounters (Benowitz, 1992; Miller and Gold, 1994; Harzke et al., 2008). These episodes of excessive drug intake can be modeled in the laboratory by giving subjects unlimited-access to a drug during 12- to 24-h test sessions. During these sessions, animals will exhibit high levels of drug intake that are associated with a loss of circadian patterns of motor activity, a dysregulation of homeostatic autonomic functions, and acute withdrawal symptoms upon session termination (Mutschler and Miczek, 1998; Tornatzky and Miczek, 2000; Fowler et al., 2007). Recently, Smith et al. (2011b) reported that exercise reduces cocaine intake during a 23-h period of unlimited drug access. In that study, male and females rats were assigned to sedentary and exercising conditions at weaning and implanted with intravenous catheters after 6 weeks. Once self-administration was acquired, rats were given unlimited, 23-h access to cocaine at 72-h intervals. Exercising rats had access to their running wheels in their home cage, but wheels were not available during the test sessions. Exercising rats self-administered significantly less cocaine than sedentary rats during the 23-h test sessions, and this effect was apparent in both males and females and across multiple doses of cocaine. Analysis of within-session data from individual rats revealed that these differences were due to differences in the duration of responding between the two groups, with exercising rats terminating their binge an average of 2.3 h sooner than sedentary rats. These data suggest that aerobic exercise could protect against binge-like patterns of excessive drug intake under unlimited-access conditions, and may be an effective treatment intervention in populations reporting high rates of compulsive substance use.

RELAPSE AND REINSTATEMENT

One final feature of substance use disorders that presents a major and persistent obstacle to long-term recovery is relapse to drug use after a period of abstinence. Previous studies report that up to 70% of recovering substance abusers relapse to drug use within 1 year after initiating treatment (Carroll et al., 1994). Although multiple variables contribute to the likelihood of relapse, two factors have been examined in the context of exercise: environmental stimuli associated with drug use (i.e., cues) and direct exposure to the substance itself. In the laboratory, the reinstatement procedure has been used to successfully model relapse to drug use and drug-seeking behavior after exposure to drug-paired stimuli (i.e., cue-induced reinstatement) and non-contingent drug administration (i.e., drug-primed reinstatement). Tests of cue-induced and drug-primed reinstatement are typically preceded

by a period of time during which responding is extinguished by withholding the drug and/or drug-related cues. An increase in responding after non-contingent drug or cue exposure is seen as mimicking a return to drug use after a period of abstinence, thus modeling the cardinal feature of relapse in substance-abusing populations. In a recent study, Zlebnik et al. (2010) reported that concurrent access to a running wheel decreased responding during extinction and cocaine-primed reinstatement in female rats. Notably, only a single session of wheel exposure was necessary to reduce cocaine-primed reinstatement, suggesting that the effects of exercise on drug-seeking behavior were immediate under these conditions. Similarly, Lynch et al. (2010) reported that access to a running wheel in the home cage during a 14-day period of forced abstinence was sufficient to reduce both subsequent extinction and cue-induced reinstatement responding in male rats, suggesting that the effects of running last beyond a particular bout of exercise. Consistent with both studies, Smith et al. (2011a) reported that long-term access to a running wheel in the home cage (6 weeks before initial drug exposure plus an additional 3 weeks after initial drug exposure) was sufficient to reduce extinction responding, cocaine-primed reinstatement, and cue-induced reinstatement in both male and female rats. Although females tended to exhibit higher levels of responding than males, exercise was an effective intervention in both sexes. Collectively, these data suggest that exercise may reduce drug-seeking behavior after a period of abstinence and may be effective at preventing relapse in treatment-seeking populations.

THE EFFECTS OF EXERCISE ON DRUG SELF-ADMINISTRATION: OTHER DRUGS

A limited number of self-administration studies have examined the effects of exercise on drug intake with drugs other than cocaine and the amphetamines. Several studies have described the effects of exercise on ethanol self-administration, and a mixed pattern of results have been reported. In an early study, McMillan et al. (1995) reported that concurrent access to a running wheel decreased ethanol consumption in alcohol-preferring rats under conditions in which consumption of ordinary tap water was increased. Ehringer et al. (2009) reported that concurrent access to a running wheel decreased alcohol consumption in laboratory mice using an unlimited-access, two-bottle choice procedure; however, exercise failed to decrease ethanol consumption in a limited-access, drinking-in-the-dark procedure modeling binge-like drinking patterns. In contrast to these results, Werme et al. (2002) reported that rats with access to a running wheel during a 1- or 2-week ethanol withdrawal period consumed more ethanol than a group of sedentary control rats when ethanol was reintroduced. Meanwhile, other studies reported no effect of voluntary wheel running on ethanol consumption (Crews et al., 2004; Ozburn et al., 2008). Many of these contrasting effects can be explained by procedural differences across the various studies, but additional research will be needed before conclusions can be made about the potential efficacy of exercise-based interventions in alcohol-abusing populations.

In contrast to that obtained with ethanol, a consistent pattern of effects is emerging from the opioid literature. Hosseini et al. (2009) used a forced exercise procedure to examine the effects of exercise on opioid self-administration. In rats with no prior history of drug self-administration, running on a treadmill for 90 min/day for 30 consecutive days reduced responding maintained by a moderate dose of morphine. In support of these findings, Smith and Pitts (2011a) reported protective effects of exercise on heroin self-administration. In that study, voluntary wheel running in the home cage for 9 weeks (8 weeks before initial heroin exposure plus 1 week after initial heroin exposure) decreased responding maintained by an extensive range of heroin doses. These data suggest that aerobic exercise may decrease the positive reinforcing effects of mu opioid agonists and may be an effective intervention in opioid-abusing populations.

Although the vast majority of the work on the effects of exercise in humans has focused on nicotine/tobacco, very few studies have examined the parallel in animal studies. However, preliminary findings from reinstatement procedures indicate that exercise effectively decreases nicotine-seeking behavior in laboratory animals. Sanchez et al. (2011) examined the effects of daily exercise during abstinence from extended access nicotine self-administration (23 h/day, for a total of 10 days) on subsequent nicotine-seeking behavior. Given that humans who smoke generally begin smoking during adolescence, rats were also given access to nicotine during adolescence (beginning on postnatal day 28). During the abstinence period, half the group had daily access to an unlocked wheel for 2 h/day ($N = 10$) and the other half had access to a locked wheel for 2 h/day (sedentary controls; $N = 11$). Nicotine-seeking, as assessed under a cue-induced reinstatement paradigm, was then examined in rats after abstinence (i.e., following 2 weeks, when nicotine-seeking is known to be high). Results showed that wheel running significantly reduced subsequent responding during extinction, although its effects on reinstatement were variable. Nonetheless, these preliminary findings are consistent with those observed in humans and suggest that the use of animal models may be useful for determining the mechanisms for the efficacy of exercise as a relapse intervention for nicotine dependence.

MECHANISMS OF EXERCISE ON DRUG SELF-ADMINISTRATION: BEHAVIOR

A number of behavioral/psychological mechanisms likely contribute to the beneficial effects of exercise on measures of drug self-administration. First and foremost, exercise serves as an alternative, non-drug reinforcer to decrease drug self-administration. The ability of alternative non-drug reinforcers to attenuate measures of drug self-administration has been well-described in the literature and may take the form of consumable, possessional, or activity-based stimuli (see reviews by Carroll, 1993; Higgins, 1997). Most studies examining non-drug reinforcers typically provide the drug and non-drug stimuli on a concurrent schedule of reinforcement, a type of operant contingency in which two options are simultaneously available and the subject chooses how to allocate its behavior to the two response alternatives. It is important to note that in studies in which exercise was used as an alternative reinforcer, the decrease in drug self-administration could not be attributed to simply having less time available to self-administer the drug. In all existing studies, test sessions lasted several hours or longer (e.g., Kanarek et al., 1995; Cosgrove et al., 2002; Zlebnik

et al., 2010; Miller et al., 2011), and the cumulative amount of time spent on both activities was less than the total duration of the session. Consequently, the ability of exercise to decrease drug self-administration is generally attributed to a decrease in the relative reinforcing strength of the drug when both are concurrently available.

Exercise may also decrease drug self-administration by decreasing comorbid risk factors that are associated with substance use disorders. There is a large body of literature indicating that exercise decreases measures of depression and anxiety in human populations (see reviews by Herring et al., 2010; Perraton et al., 2010), both of which are risk factors for substance use and abuse (Swendsen and Merikangas, 2000; Castle, 2008). Manipulations that increase depression and anxiety in animal models also increase measures of drug self-administration (Holmes et al., 2002; Richards et al., 2009), and exercise reliably decreases depression and anxiety in these animal models (Fulk et al., 2004; Zheng et al., 2006). Exercise also normalizes the behavioral and neurobiological consequences of prolonged stress in laboratory animals (Haack et al., 2008; Marais et al., 2009), which is another risk factor for substance abuse in humans. Exercise may thus be producing some its protective effects in animal models by reducing negative affective states that serve to initiate, maintain, and accelerate drug self-administration.

In human populations, exercise increases measures of well-being, self-esteem, and self-efficacy under some conditions (Fillipas et al., 2006; Muller et al., 2006; Hughes et al., 2010). These positive affective states are negatively correlated with substance use (Ellickson and Hays, 1991; Griffin et al., 2001; Zamboanga et al., 2009), and may offer protection against developing a substance use disorder. As reviewed above, aerobic exercise produces positive affective states in laboratory animals, but the nature of these effects are less clear. Animal models of self-esteem and self-efficacy are ill-defined, but it is universally accepted that exercise is good for the well-being of laboratory animals, as indicated by measures of physical health and longevity (Goodrick, 1980; Radák et al., 2001; Pinheiro et al., 2007). Although experimental evidence will be difficult to obtain, exercise may decrease drug self-administration in animal models by producing the same positive affective states as it produces in humans.

MECHANISMS OF EXERCISE ON DRUG SELF-ADMINISTRATION: NEUROBIOLOGY

Accumulating evidence shows that exercise influences many of the same signaling molecules and neuroanatomical structures that mediate the positive reinforcing effects of drugs. For instance, several neurotransmitters controlling drug self-administration are modulated by both acute and chronic bouts of exercise. The positive reinforcing effects of many drugs of abuse, including stimulants, opioids, and alcohol, are mediated, in part, by increases in the concentration of the catecholamine dopamine in the nucleus accumbens (Leshner and Koob, 1999). Importantly, acute bouts of exercise increase central concentrations of dopamine (Meeusen and De Meirleir, 1995), and chronic bouts of exercise alter the expression of several dopamine binding proteins (MacRae et al., 1987; Fisher et al., 2004). Norepinephrine, another catecholamine neurotransmitter, plays a critical role in relapse to drug use after a period of abstinence. Preclinical studies report the norepinephrine is important for both stress-induced and cocaine-primed reinstatement in animal models (Erb et al., 2000; Zhang and Kosten, 2005). Exercise decreases norepinephrine release in the frontal cortex (Soares et al., 1999), which may serve to attenuate the effects of stress and cocaine in reinstatement procedures. In addition to the catecholamines, repeated exposure to drugs of abuse decreases basal levels of the amino acid glutamate, but increase the response of glutamate to drug administration (Schmidt and Pierce, 2010). These changes in glutamate signaling play a critical role in mediating drug seeking and relapse after chronic drug exposure (Kalivas, 2009). In models of ischemia, which results from the excessive release of glutamate and overstimulation of glutamate receptors, exercise normalizes glutamate signaling, blocking the increase in glutamate caused by ischemic injury, and improving functioning (Jia et al., 2009). Because chronic drug exposure produces similar effects to ischemia on glutamate signaling, exercise may attenuate drug-seeking behavior in relapse and reinstatement procedures by attenuating the response of glutamate produced by non-contingent drug administration and/or exposure to drug-associated cues. Finally, exercise increases plasma concentration of endogenous opioid peptides that bind to all three major opioid receptor subtypes (i.e., mu, kappa, delta; Aravich et al., 1993; Art et al., 1994; Fontana et al., 1994; Debruille et al., 1999; Chen et al., 2007). Chronic exercise produces alterations in opioid binding proteins (Houghten et al., 1986; de Oliveira et al., 2010), and decreases sensitivity to exogenously administered opioid agonists (Kanarek et al., 1998; Smith and Yancey, 2003; Smith and Lyle, 2006). The ability of exercise to decrease morphine and heroin self-administration is likely mediated by changes in central opioid receptor populations after extended periods of aerobic activity. Studies have shown that the opioid receptor system also plays an important modulatory role in the reinforcing effects of cocaine (Mello and Negus, 2000) and alcohol (Walker et al., 2011). Release of endogenous opioid peptides may thus be one way exercise produces generalized protective effects on drug self-administration across multiple pharmacological classes.

In addition to several neurotransmitters, multiple intracellular signaling molecules that are involved in drug self-administration are also influenced by physical activity and exercise. For instance, repeated cocaine administration upregulates D1-mediated cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling, and the reinforcing effects of dopamine agonists are positively correlated with their ability to stimulate cAMP production. Direct activation of PKA increases cocaine self-administration (Lynch and Taylor, 2005), whereas inhibition of PKA decreases cocaine self-administration and subsequent drug-seeking behavior during reinstatement (Lynch and Taylor, 2005; Sanchez et al., 2010). Importantly, this intracellular signaling pathway is also influenced by exercise. Mice selectively bred for high levels of wheel running have lower levels of transcripts encoding adenylate cyclase subtypes and activating polypeptides in the striatum relative to controls. Exercise also modulates dopamine cAMP-regulated neuronal phosphoprotein (DARPP-32; Aguiar et al., 2010), a target of PKA that is essential for drug reinforcement (Svenningsson et al., 2005). Extracellular signal-regulated kinase (ERK) is another intracellular signaling molecule involved in drug

reinforcement that is influenced by exercise. Levels of ERK in the nucleus accumbens are correlated with drug self-administration and drug-seeking behavior across a number of different drugs, including stimulants (Lu et al., 2006; Koya et al., 2009; Lynch et al., 2010; Edwards et al., 2011), opioids (Li et al., 2008), and alcohol (Schroeder et al., 2008). Moreover, phosphorylated levels of ERK increase over an abstinence period, and these increases may serve to enhance responding in reinstatement procedures. Exercise blocks the increase in phosphorylated levels of ERK associated with enhanced cocaine-seeking behavior after a period of abstinence, and decreases reinstatement responding following exposure to drug-associated cues (Lynch et al., 2010). Finally, brain-derived neurotrophic factor (BDNF) is an intracellular signaling molecule mediating synaptic plasticity that is linked to both drug reinforcement and exercise. BDNF concentrations increase in mesolimbic structures over an abstinence period and are associated with progressive increases in drug-seeking behavior after withdrawal (i.e., Grimm et al., 2003). Exercise elevates BDNF throughout brain and modulates chromatin structure containing the BDNF gene via epigenetic mechanisms (Gomez-Pinilla et al., 2011). Exercise may normalize some of the synaptic changes caused by repeated drug administration by normalizing BDNF signaling in those structures responsible for drug reinforcement.

One additional mechanism by which exercise may modulate drug self-administration and drug-seeking behavior is by producing neuroanatomical changes via neurogenesis and gliogenesis. Aerobic exercise reliably induces neurogenesis in several regions of the hippocampus (Rhodes et al., 2003; Uda et al., 2006). Reductions in hippocampal neurogenesis have been implicated in drug self-administration (Noonan et al., 2010); and by extension, exercise may enhance the ability of this structure to buffer against compulsive patterns of drug intake. Aerobic exercise also increases gliogenesis in the prefrontal cortex of rats (Mandyam et al., 2007), and exercise has positive effects on prefrontal-dependent behavior in humans (Small et al., 2006; Yanagisawa et al., 2010). Deficits in prefrontal functioning play a contributing role in several different transitional stages of drug abuse and dependence (Goldstein and Volkow, 2002) and may play a role in relapse to drug use after a period of abstinence (Van den Oever et al., 2010). Similar to its effects in the hippocampus, exercise may produce its protective effects on measures of drug self-administration by enhancing the ability of the prefrontal cortex to function as a buffer against maladaptive patterns of drug use.

FUTURE DIRECTIONS AND TRANSLATIONAL IMPLICATIONS

Although data obtained in laboratory animals are promising, a number of areas remain unexplored, and further preclinical research will be necessary to guide the development of clinical interventions. Most notably, the effects of exercise on the self-administration of many common and emerging drugs of abuse remain undetermined. For instance, cannabis is the most commonly used illicit drug in the United States and Europe, yet few studies have examined how exercise impacts its effects. Similarly, no studies have examined exercise and many of the increasingly popular designer drugs, such as the synthetic cannabinoids (e.g., "Spice," "K2") and novel amphetamine derivates (e.g., mephedrone). It also is not clear when exercise needs to occur in relation to drug exposure for maximal benefits to be obtained. Studies in which exercise was concurrently available as an alternative, non-drug reinforcer suggest that exercise need not be initiated prior to drug exposure to be effective (e.g., Zlebnik et al., 2010); however, other studies report that exercise during an early critical period in development might offer long-term protection (Smith et al., 2008). It also remains to be determined how much exercise is necessary for beneficial effects to be obtained. For example, it is not clear whether full protection is achieved once a threshold level of exercise has been achieved or whether increasing levels of protection are obtained with increasing levels of exercise. Forced exercise procedures, which allow the intensity and duration of exercise to be experimentally manipulated, may be able to resolve this issue. One potential problem with forced exercise is that it often functions as a stressor (e.g., Moraska et al., 2000), which can confound measures of drug self-administration.

Additional research is also needed on potential sex differences in the effects of exercise on drug self-administration. In the only study that reported sex differences, concurrent access to a running wheel decreased cocaine self-administration in both males and females, but this effect was only significant in females (Cosgrove et al., 2002). Two other studies reported no sex differences in the effects of exercise on measures of escalation, binge responding, extinction responding, drug-primed reinstatement, and cue-induced reinstatement (Smith et al., 2011a,b). Gonadal hormones are known to influence both drug self-administration (Roberts et al., 1989; Feltenstein and See, 2007; Larson and Carroll, 2007; Mello et al., 2011) and wheel running (Hertrampf et al., 2006; Hydock et al., 2007), but it is not known whether gonadal hormones influence the effects of exercise on drug self-administration. Studies that experimentally manipulate the hormonal milieu via gonadectomy and receptor-specific antagonists will be necessary to characterize the role of sex-specific hormones in this relationship.

Further investigation is also needed on the mechanisms by which exercise decreases drug self-administration. Although the ability of exercise to serve as an alternative, non-drug reinforcer is well-established, the behavioral processes contributing to this effect is not known. Further parametric manipulations are needed to determine whether exercise and drug self-administration function as substitute reinforcers, and whether choice between the two alternatives are sensitive to price (e.g., unit dose) and income (e.g., session length) manipulations. There is now a wealth of information on the neurobiological effects of exercise; however, it is less clear which of these many effects contribute to its ability to decrease drug self-administration. Studies that target specific proteins through site-specific antagonists, genetic knockouts/knockdowns, and antisense oligonucleotides should shed additional light on which neurotransmitters and intracellular signaling molecules are responsible for exercise's protective effects.

To date, preclinical studies have focused almost entirely on aerobic forms of exercise, and the beneficial effects of other types of exercise are not known. The effects of resistance exercise and strength training remain unexplored, and new lines of research are greatly needed in this area. Whereas the effects of exercise as a potential monotherapy have been the subject of intense investigation, its efficacy with other interventions has not been systematically addressed. Given that clinicians will implement

exercise-based interventions in combination with other behavioral therapies and pharmacotherapies, additional research will be needed to determine how exercise interacts with these treatments. Finally, almost all the studies conducted so far have been in laboratory rats, and the relevance of potential species differences has not been tested. Additional animal models, including those using non-human primates, will be needed to guide the development of clinical interventions targeting human populations.

Despite these unanswered questions, much is already known about the effects of exercise on drug self-administration, and some tentative recommendations for its translation into clinical practice can be made. First, any amount of exercise is likely to be beneficial. Although preclinical studies describing the correlation between measures of exercise output and drug self-administration are mixed, consistent group differences between sedentary and exercising subjects are almost universally reported. Second, exercise is likely to have therapeutic effects in both men and women. Preclinical studies have consistently reported positive responses in both males and females, and potential sex differences are likely to reflect the degree to which exercise is effective in a given population. Third, early exposure to exercise is likely to have long-term protective effects. Studies show that many of the neurobiological effects of exercise develop over time, and earlier interventions may be necessary to achieve maximal protective effects. Fourth, exercise is likely to have beneficial effects even after a history of chronic inactivity. Multiple studies report that exercise is effective at reducing drug self-administration when initiated only after regular patterns of drug intake have been established – a period of time analogous to that experienced by clinical populations undergoing formal treatment. Fifth and finally, exercise is likely to be effective as both a preventative and treatment intervention. Studies conducted with cocaine indicate that exercise has protective effects during all transitional stages of substance use and abuse, including the acquisition of drug use, the maintenance of stable patterns of drug use, the escalation of drug use over time, the compulsive patterns of drug use evident during a binge, and the relapse to drug use after a period of abstinence.

CONCLUSION

The preclinical data describing the effects of exercise on drug self-administration are highly promising. The effects of exercise on cocaine self-administration are well-established, and significant data have been obtained for other drugs as well. Many of the neurobiological effects of exercise have been characterized, and the ability of exercise to serve as an alternative, non-drug reinforcer, and decrease comorbid risk factors associated with substance use has been demonstrated across multiple assays. Further research is needed to determine the optimal parameters necessary to maximize the protective effects of exercise, but enough is now known to begin the process of designing and implementing exercise-based interventions in clinical and at-risk populations.

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