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Aerobic exercise attenuates reinstatement of cocaine-seeking behavior and associated neuroadaptations in the prefrontal cortex

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Abstract

Background—Exercise has recently been suggested as an attractive alternative to pharmacotherapy for treating drug addiction. The goal of the current study was to determine using an animal model whether aerobic exercise may block reinstatement of cocaine-seeking and its underlying neurobiology (i.e., neuronal signaling in the prefrontal cortex).

Methods—Following acquisition and 10 days of 24-hr access to cocaine (1.5 mg/kg/infusion) or saline under a discrete trial procedure (4 infusions/hr), rats began a 14-day abstinence period. During this period, rats were either given access to a running-wheel for 2-hours each day or placed in similar boxes with the wheel locked. Cocaine-seeking was assessed following the 14th day of abstinence using a within-session extinction/cue-induced reinstatement procedure. Neuronal activity was assessed by examining phosphorylated levels of extracellular signal-regulated kinase (pERK) using Western Blot analysis.

Results—Wheel running reduced cocaine-seeking during both extinction and reinstatement. Cocaine-seeking was positively associated with pERK levels in the prefrontal cortex. While pERK levels were not different among saline controls, in the cocaine group pERK levels were significantly decreased by exercise.

Conclusion—Aerobic exercise may reduce relapse vulnerability by preventing the increase in cocaine-seeking and associated neuroadaptations in the prefrontal cortex that develop over an abstinence period.

Keywords

exercise; addiction; cocaine; extracellular signal-regulated kinase (ERK); incubation; neuroadaptations

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Introduction

Drug relapse following prolonged abstinence is often precipitated by re-exposure to cues previously associated with the drug. While pharmacotherapies are currently used to prevent this craving in opiate, tobacco, and alcohol addiction, none have been approved for cocaine addiction (1). Numerous pharmacotherapies have been examined, particularly compounds that interact with the dopaminergic reward system, and while some of these compounds have shown promise for treating cocaine addiction, their efficacy has proved variable and side effects have often limited compliance. One non-pharmacological alternative that also interacts with the dopaminergic reward pathway is exercise. Exercise activates the same reward pathway as cocaine, through increases in dopamine concentrations (2–3) and dopamine receptor binding (4), therefore exercise may protect against cocaine relapse by countering neuroadaptations in dopaminergic signaling following chronic exposure.

Although exercise as a therapy for cocaine addiction has not been well studied, recent data in smokers suggest that it may be a useful intervention for addiction. Aerobic exercise has been shown to alleviate withdrawal symptoms, decrease smoking, and reduce levels of craving (5). It has also been reported to alleviate depression and reduce measures of anxiety (5–6), factors known to contribute to cocaine-craving and relapse in humans (7). Animal studies have shown that exercise reduces the cocaine's reinforcing effects (8), with recent results showing that it reduces cocaine-seeking when exercise is concurrently available (9). It is not yet known whether exercise during abstinence may be useful for preventing subsequent craving and relapse.

Here we used an animal model to determine whether aerobic exercise during abstinence may block subsequent cocaine-craving and its underlying neurobiology. Like the human situation where cocaine-craving is reported to increase over the first several weeks of abstinence (10), drug-seeking behavior also increases, or incubates, over an abstinence period in animals (11). Recent evidence indicates that neuronal activity in the prefrontal cortex (PFC) is critically involved in incubation of cocaine-craving. Specifically, Koya et al. (12) showed that incubation of cocaine-craving was positively correlated with levels of phosphorylated extracellular signal-regulated kinase (pERK) (a marker of neuronal signaling which requires coincident activation of dopamine and glutamate signaling) in the PFC, and that direct inhibition of the ventral medial PFC resulted in decreased cocaine-seeking behavior. Here we hypothesized that wheel running, a form of aerobic exercise that is reinforcing in rats (13), would attenuate both cocaine-seeking and neuronal signaling in the PFC following abstinence from cocaine self-administration.

Methods and Materials

Procedures (Figure 1A) for cocaine self-administration, cue-induced reinstatement, and Western blot analysis were conducted as previously described (14,15) and as detailed in the Supplement. Briefly, male (N=21) Sprague-Dawley rats were trained to self-administer cocaine infusions (1.5 mg/kg) under a fixed-ratio 1 schedule of reinforcement (i.e., each lever press resulted in a delivery of drug). Following acquisition, rats were given 24-hour access to cocaine under a discrete trial procedure (4 trials/hour) for ten consecutive sessions. Following the last cocaine self-administration session, rats began a fourteen day abstinence period during which they were either given free access to a running wheel for 2-hrs/day or access to a locked running wheel for 2-hrs/day, as detailed in Supplement. Reinstatement of responding was then examined following the fourteenth day of abstinence using a within-session extinction/cue-induced reinstatement procedure. Additional groups of sedentary (n=7) and exercising (n=8) rats were given access to saline infusions using identical experimental procedures as used for cocaine self-administration and as detailed in

Supplement. Following the completion of the experiment, rats were sacrificed by rapid decapitation, and the medial PFC (including both ventral and dorsal) was dissected and processed for Western blot analysis of ERK. Data were analyzed by ANOVA, as detailed in the Supplement.

Results

Although total daily cocaine intake did not differ between the exercise and sedentary groups over the 10 24-hr discrete trial cocaine self-administration sessions (See Supplement: Figure S1; Group effect; $F_{(1,19)} = 0.02$, $P=0.90$), results showed that wheel running significantly reduced lever presses during extinction (Figure 1B, group by extinction session, $F_{(5,95)} = 2.74$, $P=0.02$). Wheel running also reduced cocaine-seeking in response to the cues formerly associated with cocaine (Figure 1C, group effect, $F_{(1,19)} = 8.22$, $P=0.01$; group by session, $F_{(1,19)} = 6.63$, $P=0.02$). Notably, the effects of exercise on reinstatement responding did not appear to depend on levels of running during the 2-hr sessions. Specifically, levels of wheel running were variable between animals ranging from 343 rotations/session to just under 4000 rotations/session (mean rotations were 1731 ± 330 rotations, or approximately, 400 meters/session). However, there was no correlation between levels of wheel running and cue-induced reinstatement ($r=0.05$) indicating that the availability of a freely moving wheel, but not levels of wheel running, predicts the reinstatement response. Among saline controls, the number of infusions obtained and subsequent levels of extinction and reinstatement responding were low and did not differ significantly between the sedentary and exercise groups (P 's > 0.05 ; data not shown). The number of wheel rotations did not differ significantly between the saline and cocaine groups ($P = 0.71$).

To understand the underlying mechanism for the effect of exercise on cocaine-seeking, markers of neuronal signaling (i.e., ERK) were examined in the PFC (See Supplement: Figure S2). Consistent with previous findings, we observed a significant positive association of pERK levels and cocaine-seeking behavior for both pERK 1 and 2 ($r = 0.52$, $P = 0.02$; $r = 0.58$, $P = 0.01$; respectively; See Supplement: Figure S3). Although total ERK levels in the PFC did not differ between the two cocaine groups (Figure 2A), rats given access to a wheel during abstinence had reduced levels of pERK as compared to sedentary rats (Figure 2B). Exercise significantly decreased phosphorylation at both ERK1 and 2, but total levels of ERK1 also tended to be lower (Figure 2A, $P = 0.08$), and the increase in percent of total protein activated was apparent only for ERK2 (Figure 2C). Among saline controls no statistically significant differences were observed between the sedentary and exercise groups for either total or phosphorylated levels of ERK (Total ERK1, $P = 0.39$; Total ERK2, $P = 0.70$; pERK1, $P = 0.63$; pERK2, $P = 0.70$; see Figure 2 D-E). As expected, total and phosphorylated levels of ERK were significantly lower in saline controls as compared to the cocaine groups (P 's > 0.05).

Discussion

Aerobic exercise as an intervention for cocaine addiction is not well studied, but it may offer a safe non-pharmacological alternative that can have secondary health benefits (e.g. prevention of obesity). Our results show that aerobic exercise during an abstinence period decreases subsequent cocaine seeking and associated neuroadaptations. We found that 2-hrs/day of exercise reduced extinction responding by approximately 35%, and attenuated cue-induced reinstatement responding by almost 50%. Exercise also decreased pERK levels, particularly at pERK2, a finding that is consistent with previous work implicating ERK2, not ERK1, in the behavioral effects of drugs of abuse (16). Since levels of pERK increase over time and are known to be associated with incubation of cocaine-craving (13; also see Supplement: Figure S3), our findings suggest that aerobic exercise during abstinence may

decrease the ability of the cocaine-associated cues to activate PFC neurons (as assessed by pERK), which in turn led to decreased subsequent cocaine-seeking. This effect does not appear to be due to a general effect of exercise on neuronal signaling in the PFC as exercise did not have an effect of neuronal signaling in the PFC among saline controls.

Although the exact mechanism remains to be determined, our current findings, in conjunction with previous findings on ERK signaling in the PFC, provide some insight into this mechanism. It is believed that both glutamate and dopamine are upstream regulators of ERK (17), with evidence to suggest that while both contribute to cocaine-craving, glutamatergic signaling in particular underlies incubation of cocaine-craving (18). Thus, in addition to the effects of exercise on dopamine, it is also possible that exercise directly affects glutamatergic signaling although information on this potential effect is lacking. Another possibility is that the effects of exercise on glutamate are indirect. For example, by mimicking the effects of cocaine through the maintenance of high dopamine levels, exercise may “reset” the time-dependent incubation clock that is known to be dependent on glutamate activation (19). An additional possibility is that access to a novel stimulating environment (i.e., running wheel) during periods of abstinence may have caused cocaine associated cues to become less salient and rats may have become less motivated to respond to them (20). Although, if our effects were due simply to an enriched environment, both groups would have shown a uniform decrease. Further studies are necessary to examine these possibilities.

Aerobic exercise has the potential to function as a treatment for relapse by blocking neuroadaptations in the PFC that develop over an abstinence period. It is unknown whether exercise can sustain these neuromodulations long-term. Nonetheless, these findings reveal neuroadaptive benefits of exercise for attenuating cocaine-seeking behavior following prolonged abstinence, and they suggest that exercise should be examined as a potential treatment for cocaine relapse either alone, or perhaps as an adjunct to pharmacotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Time-line of experimental events and the effect of aerobic exercise on cocaine-seeking. **(A) Time-line:** Following acquisition, rats were given 24/hr access to cocaine (1.5 mg/kg/infusion) under a discrete trial procedure (4 trials/hr) for a total of 10 days (“binge self-administration”). During a 14-day abstinence period that followed, 11 rats were given access to a running-wheel for 2 hours each day while another 10 rats were placed in similar boxes but the wheel was locked at all times. Cocaine-seeking was then assessed after the 14th day of abstinence when cocaine-seeking is known to be high using a within-session extinction/cue-induced reinstatement procedure. Additional groups of sedentary (n=7) and exercising (n=8) rats were given access to saline infusions using identical experimental procedures as used for cocaine self-administration. **(B) Extinction:** Exercising rats responded at lower levels during initial extinction sessions (extinction session 1; $t_{(19)} = 4.38$, $P = 0.02$), but did not differ from sedentary rats prior to reinstatement testing (extinction session 6; $P = 0.76$). **(C) Reinstatement:** Although exercising and sedentary rats did not differ prior to reinstatement testing, exercising rats responded at significantly lower levels than sedentary rats during the reinstatement session ($t_{(19)} = 5.56$, $P = 0.006$). Error bars represent SEM. An asterisk indicates a significant group difference ($P < 0.05$).

Figure 2.

(A-C) Exercise reduces ERK signaling in the PFC of rats following cocaine reinstatement. Tissue was obtained following the cocaine reinstatement test for 8 of the 11 rats in the exercising group and 7 of the 10 rats in the sedentary group. Total ERK 1 and 2 (A) and pERK 1 and 2 (B) were quantified by densitometry, and the data were normalized to tubulin. Immunoblots for detection of total ERK and pERK are shown above each respective panel. (A) Total ERK levels did not differ significantly between the exercise and sedentary groups ($P = 0.08$; ERK1, $P = 0.91$, ERK2). (B) Exercising rats had reduced levels of pERK in the PFC as compared to sedentary rats (ERK1; $t_{(13)} = 3.92$, $P = 0.04$; ERK2; $t_{(13)} = 4.43$, $P = 0.02$). (C) The ratio of pERK/total ERK was significantly decreased for ERK2 ($t_{(13)} = 4.38$, $P = 0.03$) but not for ERK1 ($P = 0.23$). An asterisk indicates a significant group difference ($P < 0.05$). (D-E) No effect of exercise on ERK signaling in the PFC among saline control animals. Tissue was obtained following the reinstatement test for 8 of the 8 rats in the exercising group and 7 of the 7 rats in the sedentary group. Total ERK 1 and 2 (D) and pERK 1 and 2 (E) were quantified by densitometry, and the data were normalized to tubulin. Immunoblots for detection of total ERK and pERK are shown above each respective panel. (D) Total ERK levels did not differ significantly between the exercise and sedentary groups (P 's > 0.10). (E) pERK levels did not differ significantly between the exercise and sedentary groups (P 's > 0.10). Error bars represent SEM.