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Running and addiction: precipitated withdrawal in a rat model of activity-based anorexia

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Abstract

Physical activity improves cardiovascular health, strengthens muscles and bones, stimulates neuroplasticity, and promotes feelings of well-being and self-esteem. However, when taken to extremes, exercise can develop into an addictive-like behavior. To further assess the addictive potential of physical activity, the present experiments assessed whether running wheel activity in rats would lead to physical dependence similar to that observed after chronic morphine administration. Active male and female rats were housed in running wheels, and inactive male and female rats, in standard cages. After adaptation to the housing conditions, active and inactive rats were given food for either one hour or 24 hours a day. Additionally, a group of inactive rats was paired the amount of food consumed on the previous day by food-restricted active rats. Active and inactive rats fed for only one hour a day decreased food intake and lost weight. Additionally, food-restricted active rats increased running wheel activity. When the body weight of food-restricted active rats reached 80% of their pre-restriction weight, physical dependence was assessed by injecting rats with 1.0 mg/kg naloxone, and observing them for symptoms of precipitated withdrawal. There was a direct relationship between the intensity of running and the severity of withdrawal symptoms. In both males and females, active food-restricted rats displayed the largest number of withdrawal symptoms, followed by the active rats given *ad libitum* access to food. In contrast, only minimal withdrawal symptoms were observed in inactive rats. These findings support the hypothesis that exercise-induced increases in endogenous opioid peptides act in a manner similar to chronic administration of opiate drugs.

Keywords

running wheels; activity-based anorexia; rats; naloxone; drug abuse; exercise

Physical activity facilitates weight control, improves cardiovascular health, strengthens muscles and bones, promotes neuroplasticity, decreases anxiety, offsets depression, and elevates mood (Brene, Bjornebekk, Aberg, Mathe, Olson, & Werme, 2006; Churchill, Galvez, Colcombe, Swain, Kramer, & Greenough, 2002; Greenwood & Fleshner, 2008; Narath 2001; Paluska & Schwenk, 2000; Smits, Berry, Rosenfield, Powers, Behar & Otto, 2008; Teychenne, Ball, & Salmon, 2008). However, despite these beneficial outcomes, when taken to extremes, physical activity can develop into an addictive-like behavior. Committed runners appear to be

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particularly susceptible to the addictive properties of exercise. Runners often report 1) a feeling or euphoria after a strenuous bout of exercise (runner's high), 2) the need to increase the distance run to achieve feelings of well-being (tolerance), 3) difficulties in job performance and social interactions (addiction) and 4) symptoms of withdrawal, including depression, irritability, and anxiety, when prohibited from running; (withdrawal) (Adams & Kirby, 2002; Aidman & Woolard, 2003; Allegre, Souville, Therme, & Griffiths, 2006).

In experimental animals, physical activity can also have dichotomous effects. There is a growing body of literature indicating that exercise has beneficial effects on behavior and brain functioning (Greenwood & Flesner, 2008; Moltini, Ying, & Domez-Pinilla, 2002; Pietropaolo, Sun, Li, Brana, Feldon, & Yee, 2008; Smith and Zigmond, 2003). However, as in non-human animals, in our own species, physical activity can transition into an addictive-like behavior, and interfere with the performance of life sustaining behaviors. For example, when rats are housed in standard cages and given food for only 1 hour a day, they quickly adapt to the food restriction schedule, increasing food intake over time, and ultimately gaining weight. In contrast, when rats are housed in running wheels and placed on the same food restriction schedule, they decrease food intake and body weight. Over time, these animals display a dramatic increase in wheel running, accompanied by continued reductions in food intake and body weight. Within seven to ten days, rats maintained on this schedule die of starvation (Boakes & Dwyer, 1997; Boakes, Mills, & Single, 1999; Kanarek & Collier, 1983; Routenberg & Kuznesof, 1967). This phenomenon has been called activity-based anorexia (ABA). As excessive exercise is a common symptom of eating disorders, particularly anorexia nervosa (Davis, Katzmann, & Kirsch, 1999; Sundgot-Borgon & Torstveit, 2004), ABA has been proposed as an animal model of the disease (Aravich, Rieg, Lauterio, & Doerries, 1993; Casper, Sullivan, & Tecott, 2008; Hebebrand, Exner, Hebebrand, Holtkamp, Casper, Remschmidt, Herpertz-Dahlmann, & Klingenspor, 2003;).

The ABA paradigm can also serve as a model of drug abuse. There is growing evidence that running and drugs of abuse activate overlapping neural systems (Ferreria, Lamarque, Boyer, Perez-Diaz, Jouvent, & Cohen-Salmon, 2006; Kanarek, Gerstein, Wildman, Mathes & D'Anci, 1998; Werme Thoren, Olson, & Brene, 2000; Ozburn, Harris, & Blednov, 2008). For example, endurance exercise stimulates the release of endogenous opioid peptides in rats and humans (e.g. Angelopoulos, 2001; Asahina, Asano, Horikawa, Hisamitsu, & Sato, 2003; Christie & Chesher, 1982; Janal, Colt, Clark, & Glusman, 1984; Okredalen, Solberg, Haugen & Opstad, 2001; Werme, Thoren, Olson, & Brene, 2000), and running in activity wheels mimics the effects of opiate drugs on pain sensitivity. Research in our laboratory and others shows that rats voluntarily running in wheels for prolonged periods of time are less sensitive to the pain-relieving properties of morphine and other opioid drugs than are rats housed in standard laboratory cages (D'Anci, Gerstein, & Kanarek, 2000; Kanarek, Gerstein, Wildman, Mathes, & D'Anci, 1998; Mathes & Kanarek, 2001; Mathes & Kanarek, 2004; Smith & Lyle, 2006; Smith & Yancey, 2003). Moreover, wheel running attenuates the rewarding effects of morphine in a conditioned place preference test (Lett, Grant, Koh, & Flynn, 2002), and augments morphine-induced sensitization of locomotor behavior (Kanarek & Mathes, unpublished data). These findings have led to the hypothesis that exercise-induced increases in endogenous opioid peptides act in a manner similar to chronic administration of opiate drugs (Kanarek & Mathes, 2007).

Prolonged use of opiate drugs leads to physical dependence as evidenced by the appearance of withdrawal symptoms when drug use ceases, or an opioid antagonist is administered. Since exercise is associated with the release of endogenous opioid peptides, the cessation of exercise or administration of an opioid antagonist to active animals could lead to symptoms of opiate withdrawal. As the release of endogenous opioid peptides is directly related to the intensity of aerobic activity (Mehl, Schott, Sarkar, & Bayly, 2000; Smith & Lyle, 2006; Smith & Yancy,

2003), withdrawal symptoms should be particularly evident when rats have experienced a rapid and pronounced increase in running wheel activity, such as observed with the ABA procedure. To evaluate the addictive properties of running, active and inactive male and female rats were injected with the opioid antagonist naloxone and observed for symptoms of precipitated withdrawal. It was hypothesized that food-restricted active rats who underwent the ABA procedure would display more severe symptoms of withdrawal than ad libitum fed active rats.

Experiment 1

Method

Animals, Housing and Dietary Conditions—Forty-four female Long-Evans rats (Charles River Laboratories, Raleigh NC), eight weeks of age and weighing between 150-175 g at the beginning of the experiment, were housed in a temperature-controlled room ($21^{\circ} \pm 2^{\circ}$ C) maintained on a 12:12 h reverse light-dark cycle (lights on: 2000 h). Rats initially were divided into two groups matched on the basis of body weight. Inactive rats ($n = 24$) were housed in standard cages, and active rats ($n = 20$), housed in Wahmann LC34 activity wheels (circumference 1.13 meters) with adjoining cages. Wheel turns were measured with a micro-switch such that only complete 360° turns were recorded. Wheel running was a voluntary activity.

All rats were given *ad libitum* access to ground Purina chow (#5001) and tap water, except as noted. Chow was presented in stainless-steel food cups with lids. The food cups were clipped to the cage floors to prevent spillage. Water was available in glass bottles fitted with drip-proof stainless-steel stoppers. Throughout the experiment, food and water intakes, body weights, and wheel revolutions were measured daily under red lights during the dark portion of the daily cycle (1200 - 1400 hr)

After seven days of acclimation to the housing conditions, food-restriction was initiated. Ten active and eight inactive rats were given food for only one hour a day (1300 – 1400 hr), while ten active and eight inactive rats continued to receive food for 24 hours a day. A fifth group of eight inactive rats was pair-fed the mean amount of food consumed on the previous day by the active rats on the restricted feeding schedule.

Precipitated Withdrawal—When the body weight of a food-restricted active rat reached 80% of its body weight measured on the day preceding the initiation of food restriction, it was tested for precipitated withdrawal. Active female rats reached criterion within 3 to 6 days. To allow for comparisons across exercise and feeding conditions, inactive rats given food for 1 hr/day or for 24 hr/day, and active rats given food for 24 hr/day rat were tested at the same time. To allow for the same duration of exposure to food restriction, inactive pair-fed rats were tested on the following day.

To precipitate withdrawal, rats were injected subcutaneously with 1.0 mg/kg naloxone HCl (Sigma-Aldrich Corp. St. Louis, MO) and then placed in a novel Plexiglas observation chamber (60 cm $\times$ 30 cm $\times$ 25 cm). Rats were observed for 1 hr for signs of withdrawal by two independent observers blind to the experimental conditions. Scores of the two observers were highly correlated, and the mean of the two scores was used for data analyses. Withdrawal symptoms were categorized using a scale modified from Gellert and Holtzman (1978) and Cicero et al. (2002). Body weights were measured preceding and 30 and 60 minutes after naloxone injections. Graded signs of withdrawal were scored as follows: body weight loss in 1 hr (1 for every 1% of weight loss), wet dog shakes (1-2 shakes = 2; 3 or 4 shakes = 3; 4 or more shakes = 4), escape attempts (2-4 attempts = 1, 5 to 9 attempts = 2, and 10 or more attempts = 3). Abnormal posture/writhing, teeth chattering, ptosis (drooping eyelids), diarrhea, profuse salivation, swallowing movements, abnormal postures, and chromodacyorrhea (red tears) were

scored for their presence and latency to first occurrence. The total withdrawal score was calculated as the sum of all of the individual withdrawal scores. Immediately following testing for withdrawal, all rats were returned to standard cages and given unrestricted access to food and water.

All procedures were approved by the Tufts University Institutional Animal Care and Use Committee

Data Analysis—Data were analyzed using SPSS 15.0 for Windows. Food intake, wheel turns, and total withdrawal scores were analyzed using either independent t-tests with activity as a between group measure or with ANOVAs with activity/feeding conditions as between group measures. Repeated measures analyses were used to determine changes in running wheel activity across time. *Post hoc* comparisons were made using Tukey's LSD test. Additionally, the withdrawal scores were analyzed using a non-parametric Kruskal-Wallis test with activity/feeding conditions as the grouping variable. *Alpha* was set at 0.05.

Results

Food Intake, Body Weight, and Wheel Revolutions Preceding the Initiation of Food Restriction—Mean daily food intake during the week preceding food-restriction did not differ as a function of activity condition (inactive rats = 19.4 ± 0.5 g/day; active rats = 19.4 ± 0.9 g/day). Body weights of active and inactive animals were similar at the start of the experiment. Moreover, weight gain during the week preceding food restriction did not differ as a function of activity conditions (inactive rats = 11.2 ± 2.0 g; active rats = 14.3 ± 2.4 g). Additionally, during the week preceding food restriction, the mean daily number of wheel revolutions did not differ between rats that were subsequently fed for either 1 or 24 hrs a day (Figure 1A).

Food Intake, Body Weight, and Wheel Revolutions After the Initiation of Food Restriction—When given food for only one hour a day, both active and inactive female rats decreased food intake and lost weight. However, neither food intake nor weight loss varied as a function of activity condition in food-restricted rats. Food intake of rats given *ad libitum* access to food did not differ as a function of activity condition.

Both food-restricted and non-food restricted active rats initially increased running. However, as determined by a significant interaction for days of running by feeding schedule ($F(3, 12) = 3.56$; $p < 0.05$), during this period, food-restricted active animals ran more than unrestricted active rats. It should be noted that after animals reached criterion and were tested for naloxone-precipitated withdrawal, they were removed from the wheels and given *ad libitum* access to food. As animals who made the most wheel turns reached the criterion sooner than rats that made fewer wheel turns, there was a decrease in running across time (Figure 1B).

Withdrawal Scores—Total withdrawal scores following injection of 1.0 mg/kg/sc naloxone varied significantly as a function of activity and feeding condition ($F(4, 39) = 15.53$; $p < 0.001$). *Post hoc* analysis showed that total withdrawal scores of food-restricted active rats were significantly greater than withdrawal scores of rats in all other groups ($p_s < 0.001$; Figure 2). As withdrawal scores can also be interpreted using a ranking system, further analysis using a non-parametric Kruskal-Wallis test showed that withdrawal scores varied significantly, with rats in the active-food restriction condition showing the highest overall withdrawal scores ($\chi^2(4) = 21.82$; $p < 0.001$).

A correlational analysis using all active rats revealed a significant positive relationship between total withdrawal scores and the number of wheel turns on the day preceding testing ($r = 0.453$, $p < 0.05$). Individual analysis for the two groups of active rats revealed that total withdrawal

scores were significantly correlated with number of wheel turns for food restricted rats ($r = 0.655$, $p < 0.05$), but not for ad libitum fed rats ($r = 0.237$, ns).

To further evaluate withdrawal, the number of animals in a group displaying each withdrawal symptom was determined (Table 1). Kruskal-Wallis tests showed that there was a significant difference in the number of animals showing teeth-chattering ($\chi^2(4)=13.72$; $p < 0.01$); ptosis ($\chi^2(4)=12.78$; $p < 0.05$); wet dog shakes ($\chi^2(4)=13.57$; $p < 0.01$), and escape attempts ($\chi^2(4)=16.58$; $p < 0.005$) with a greater number of active food-restricted animals displaying each symptom than animals in the other groups. There was a trend for abnormal posture to differ with activity condition ($\chi^2(4)=8.15$; $p < 0.086$). No other symptoms of withdrawal were observed in any of the groups of rats.

Experiment 2

Experiment 2 used male rats to evaluate potential sex differences in the effects of running wheel activity on symptoms associated with precipitated opiate withdrawal. The adaptation period to the wheels was increased for the males relative to the females. There were two reasons for this increase. In Experiment 1, running wheel activity appeared to be increasing when food-restriction was initiated. Previous studies have shown that it takes approximately 3 weeks for daily wheel running to reach stable levels (Mathes & Kanarek, 2006; Werme, Messer, Olson, Gilden, Thoren, Nestler & Brene, 2002). Therefore, to allow for the stabilization of wheel running, male rats were given 25 days to adapt to the wheels before food-restriction was instituted. Additionally, as male rats typically run less than females (Boakes, Mills & Single, 1999; Hirsch & Godkin, 1982), the longer adaptation period was an attempt to make the number of wheel turns of males more similar to that of females.

Method

Animals, Housing and Dietary Conditions—Forty male Long-Evans rats (Charles River Laboratories), weighing 175 to 200 g at the beginning of the experiment were used. As described in Experiment 1, inactive rats ($N=24$) were housed individually in standard stainless steel laboratory cages, and active rats ($N=16$) in Wahmann LC34 activity wheels with adjoining cages.

To allow for daily wheel turns to reach stable values, all rats were given *ad libitum* access to ground Purina Chow and water for 25 days. Food intakes, body weights, and wheel revolutions were measured every other day during the adaptation period. Animals then were divided into five groups as described in Experiment 1. Eight active and eight inactive rats continued to receive unrestricted access to food, while eight active and eight inactive rats were given food for only one hour a day (1300-1400 hr). The final eight inactive rats were pair-fed the mean amount of food consumed by food-restricted active rats on the previous day. Food intakes, body weights and wheel turns were measured daily after the initiation of the food restriction schedule.

When the body weight of a food-restricted active rat reached 80% of its body weight measured on the day preceding the initiation of food restriction, the rat was tested for precipitated withdrawal as described in Experiment 1. Additionally, on the same day, the appropriate number of rats from each of the other groups was tested with the exception of pair-fed inactive rats which were tested on the subsequent day.

Results

Food Intake, Body Weight, and Wheel Turns Preceding the Initiation of Food Restriction—Across the 25 day adaptation period, inactive rats consumed significantly ($p < 0.01$) more food per day than active rats (inactive rats = 28.4 ± 0.9 g; active rats = 25.1 ± 0.7

g). Rats were matched on the basis of body weight before being placed into standard cages or activity wheels (active = 355.1 ± 7.0 g; inactive = 368.0 ± 6.9 g). Body weights of male rats decreased when they were placed in activity wheels, and remained less than those of inactive rats throughout the adaptation period. The day before food restriction was initiated, inactive rats (472.3 ± 12.2 g) weighed significantly more than active rats (399.4 ± 9.7 g) ($t(38) = -4.47$, $p < 0.001$).

During the 25-day adaptation period, mean daily wheel turns increased significantly as a function of time ($F(9,54) = 11.96$, $p < 0.001$). However, prior to food restriction, wheel turns did not differ between active rats that subsequently were given food for 1 hour or 24 hours a day (Figure 3a).

Food Intake, Body Weight, and Wheel Turns After the Initiation of Food

Restriction—When given food for only one hour a day, both active and inactive rats decreased food intake and lost weight (Figures 4 and 5). There were no differences in food intake between active and inactive rats given food for 24-hours a day. Following the initiation of food restriction, the mean daily number of wheel turns for food-restricted rats increased, while the number of wheel turns for non-restricted animals did not (Figure 3b). Mean daily wheel turns for food-restricted active rats were significantly greater than those of ad libitum fed animals on days 2, 3 and 4 after food restriction ($p_s < 0.05$). After animals reached 80% of their pre-restriction weight and were tested for naloxone-precipitated withdrawal, they were removed from the wheels and given *ad libitum* food. As animals who made the most wheel turns reached the criterion sooner than rats that made fewer wheel turns, there was a decrease in running across time.

Withdrawal Scores—Withdrawal scores following injection of 1.0 mg/kg/sc naloxone varied significantly as a function of activity and feeding condition ($F(4, 39) = 7.71$; $p < 0.001$). *Post hoc* analysis showed that withdrawal scores of active food-restricted rats were significantly higher than the scores of rats in the three inactive conditions ($p_s < 0.001$; Figure 6). Moreover, withdrawal scores of active rats given food for 24 hours a day were significantly greater than those of rats in the three inactive conditions ($p_s < 0.05$).

Correlational analyses revealed no significant relationship between the number of wheel turns on the day preceding testing and total withdrawal scores.

Further analysis using a non-parametric Kruskal-Wallis test showed that withdrawal scores varied significantly, with rats in the active-food restriction condition showing the highest overall withdrawal scores ($\chi^2(4) = 19.16$; $p < 0.001$).

The number of animals in a group displaying each withdrawal symptom is shown in Table 2. Kruskal-Wallis tests showed that there was a significant difference in the number of animals in a group showing teeth-chattering ($\chi^2(4) = 11.7$; $p < 0.05$); ptosis ($\chi^2(4) = 21.65$; $p < 0.001$) and abnormal postures ($\chi^2(4) = 20.13$; $p < 0.001$) with more rats in the active-food restriction condition displaying each symptom than rats in the other conditions.

Discussion

Like rats made dependent on morphine, active male and female rats displayed symptoms of precipitated withdrawal when injected with the opioid antagonist naloxone. In contrast, withdrawal symptoms were minimal in inactive rats. In concordance with the present results, other studies have shown that administration of large doses of naloxone (10 mg/kg) led to greater withdrawal scores in active than inactive rats that had previously received a variety of opiate agonists (Smith & Yancey, 2003). However, it is important to note, that in the present

studies, active rats displayed symptoms of withdrawal even though they had not previously been exposed to opiate agonists, and had received a dose of naloxone (1 mg/kg) commonly used to precipitate opiate withdrawal.

Sex differences have been observed in both running wheel activity and sensitivity to opiate drugs. With respect to wheel running behavior, females typically have been reported to run more than males (Boakes, Mills, & Single, 1999; Hirsch, Ball, & Godkin, 1982). In comparison, females have usually been found to be less sensitive to opiate drugs than males (Craft, Stratmann, Bartok, Walpole, & King, 1999). In the present experiments, female rats ran more than males. Upon receiving access to the wheels, female rats made approximately 4000 wheel turns per day, while males averaged only 1000 wheel turns per day. With time, wheel running increased in both males and females. Specific comparisons between maximum levels of wheel running in non-food restricted males and females can not be made because females ran for only seven days preceding food-restriction, while males ran for 25 days. However, by day seven, females were averaging 13,000 wheel revolutions per day while males were averaging only 5500 wheel revolutions. During the initial days of food restriction, females increased running to approximately 24,000 wheel revolutions per day, while males increased to 9000 revolutions per day. Despite the differences in activity levels, food-restricted active male and female rats both displayed symptoms of precipitated withdrawal when injected with naloxone. Total withdrawal scores of food-restricted active females were slightly higher than those of food-restricted active males. However, it can not be determined if this observation reflects genuine sex differences, the greater level of running in females than in males, or if it merely occurred by chance.

One issue that should be mentioned is the possible confound between activity levels, food intake and body weight. Food-restricted active rats not only ran more, but also ate less and weighed less than *ad libitum* fed active animals. Thus, it is possible that withdrawal symptoms observed in active food-restricted rats were a function of decreased food intake or body weight rather than increased running. With respect to food intake, this seems unlikely as neither food-restricted nor pair-fed inactive rats displayed symptoms of precipitated withdrawal. With respect to body weight, it is more difficult to reach a conclusion, as active food-restricted rats did weigh less than animals in any of the other groups. However, in male rats, at the time of testing for precipitated withdrawal there were no differences in body weight between *ad libitum* fed active rats and food-restricted inactive rats. Yet, symptoms of withdrawal were much more pronounced in the *ad libitum* fed male active rats than in food-restricted inactive male rats. To more directly determine the effects of reduced body weight on symptoms of precipitated withdrawal, future studies will employ a group of inactive animals whose body weight is paired to that of active food-restricted animals.

The present findings support the hypothesis that exercise-induced increases in endogenous opioid peptides act in a manner similar to chronic administration of opiate drugs. This hypothesis was generated by studies demonstrating that chronic exercise facilitates the development of tolerance to the pain-relieving properties of opiate analgesics (Kanarek, Gerstein, Wildman, Mathes & D'Anci, 1998; Mathes & Kanarek, 2001; Mathes and Kanarek, 2006; Smith & Lyle, 2006), produces cross-tolerance to the rewarding effects of morphine (Eisenstein & Holmes, 2007; Lett, Grant, Koh, & Flynn, 2002) and sensitizes rats to opiate-induced increases in both locomotor and feeding behaviors (Mathes and Kanarek, unpublished data). Exercise-induced alterations in opioid-mediated behaviors appear to be directly related to the intensity of running. For example in the present study, female rats who ran more as a function of food restriction displayed more pronounced symptoms of naloxone-precipitated withdrawal than *ad libitum* fed active rats. Similarly, in previous studies, the development of tolerance to morphine's pain relieving actions was enhanced in rats that naturally ran more (Smith & Lyle, 2006), or who ran more as a result of food restriction (Kanarek & Mathes,

2007) than in rats who had lower levels of activity. The relationship between the intensity and behavioral consequences of running likely mirrors the positive correlations which have been observed between the intensity of aerobic activity and the release of endogenous opioid peptides (Goldfarb, Hatfield, Armstrong, & Potts, 1990; Goldfarb, Jamurtas, Kamimori, Hegde, Ottersletter & Brown, 1998).

Similarities between the effects of exercise and drugs of abuse extend beyond opiate drugs. Research demonstrating that animals will perform operant responses to obtain access to either drugs of abuse (Koop & Kreek, 2007), or a running wheel (Belke, 2004; Collier & Hirsch, 1971; Iversen, 1993) provides evidence of the rewarding properties of both drugs of abuse and running. Moreover, under certain circumstances, such as food deprivation, both drug self-administration (Campbell & Carroll, 2000); and running escalate and become maladaptive behaviors. These findings suggest that running may be able to substitute for drug taking behavior. In support of this suggestion, rats running in activity wheels self-administered smaller quantities of opiates, alcohol, and psychomotor stimulants (e.g. amphetamine and cocaine) than rats housed in standard cages (Cosgrove et al., 2002; Kanarek, Marks-Kaufman, D'Anci & Przypek, 1995; McLachlan, Hay, & Coleman, 1994; McMillian, McClure, & Hardwick, 1995).

The previous results strengthen the proposal that running and drugs of abuse activate similar neural pathways. More specifically, it has been proposed that the rewarding properties of both running and drugs of abuse are related to the activation of the dopaminergic reward pathways (Brene, Bjornebekk, Aberg, Mathe, Olson, & Werme, 2007; Smith, Schmidt, Iordanou, & Mustroph, 2007; Werme, Messer, Olson, Gilden, Thoren, Nestler & Brene, 2002). In support of this proposal, both running and drugs of abuse increase dopamine release within the reward pathways, augment central dopamine levels, and alter dopamine binding (Foley, Le, Greenwood, Strong, Breindel, & Fleshner, 2008; Smith, Schmidt, Iordanou, & Mustroph, 2008). Additionally, like drugs of abuse, running wheel activity increases levels of Δ FosB within the nucleus accumbens, while overexpression of Δ FosB in striatal dynorphin neurons enhances both running and drug self-administration (Werme, Messer, Olson, Gilden, Thoren, Nestler, & Brene, 2002). The rewarding properties of exercise may be mediated through direct activation of dopamine pathways or indirect activation through the endogenous opioid system. Both running and drug-self administration can increase β -endorphin which activates the endogenous opioid system, and consequently stimulates dopaminergic activity. In support of this latter possibility, both chronic cocaine administration and running wheel activity lead to upregulation in dynorphin mRNA in the medial caudate putamen of rats (Werme, Thoren, Olson, & Brene, 2000).

The finding that symptoms resembling those of opioid-withdrawal occur in food-restricted active rats may have correlates in clinical populations. Excessive exercise is a common symptom of eating disorders, particularly anorexia nervosa (Bamber, Cockerill, Rodgers, & Carroll, 2003; Davis & Claridge, 1998; Davis, Katzmann, & Kirsch, 1999). Initially, physical activity is used as a means of weight control, but with time can become an end in itself. In the extreme, individuals with eating disorders can have difficulty refraining from exercise despite adverse physical consequences (e.g. an unhealthy decrease in body weight; decreased bone density; stress fractures). Additionally, symptoms reminiscent of drug withdrawal, including anxiety, depression, and irritability often develop when these individuals are unable to exercise (Adams & Kirby, 2002; Aidman & Woolard, 2003; Allegre, Souville, Therme, & Griffiths, 2006). The high comorbidity of drug abuse and eating disorders (Conason, Klomek, & Sher, 2006; Franko, Dorer, Keel, Jackson, Manzo, & Herzog, 2008) provides further evidence of a common neurobiological basis for these disorders.

In conclusion, the results of the present experiment demonstrate that excessive running shares similarities with drug-taking behavior. Following naloxone injections, drug-naïve food-restricted active rats displayed symptoms of withdrawal similar to those observed in rats addicted to morphine. Taking these findings in conjunction with results of studies demonstrating that intake of drugs of abuse and running activates the endogenous opioid and dopamine reward systems suggest that it might be possible to substitute drug-taking behavior with naturally rewarding behavior.

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Figure 1.
Mean daily number of wheel revolutions preceding food restriction (A) and during food restriction (B) in female rats given food for 24-hours or 1-hour per day.

Figure 2.

Total withdrawal scores following injections of 1.0 mg/kg/sc naloxone in active and inactive female rats given food for 24-hours or 1-hour per day or inactive female rats pair-fed to active food-restricted female rats. Withdrawal scores not sharing a common letter are significantly different from each other.

Figure 3.
Mean daily number of wheel revolutions preceding food restriction (A) and during food restriction (B) in male rats given food for 24-hours or 1-hour per day.

Figure 4. Mean daily food intake on the day preceding food restriction (A) and during food restriction (B) in active and inactive male rats given food for 24-hours or 1-hour per day, or inactive male rats pair-fed to active food-restricted males.

Figure 5. Mean daily body weight on the day preceding food restriction (A) and during food restriction (B) in active and inactive male rats given food for 24-hours or 1 hour per day, or inactive male rats pair-fed to active food-restricted males.

Figure 6. Total withdrawal scores following injections of 1.0 mg/kg/sc naloxone in active and inactive male rats given food for 24-hours or 1-hour per day or inactive male rats pair-fed to active food-restricted female rats. Withdrawal scores not sharing a common letter are significantly different from each other.

Table 1
Number of Female Rats Displaying Individual Withdrawal Symptoms as a Function of Exercise and Feeding Conditions

	Teeth Chattering	Ptosis	Abnormal Postures	Wet Dog Shakes	Escape Attempts
Active + 1 hour food intake	6/10	5/10	3/10	5/10	8/10
Active + ad libitum food intake	2/10	3/10	3/10	4/10	2/10
Inactive + 1 hour food intake	1/8	0/8	0/8	0/8	4/8
Inactive + ad libitum food	0/8	0/8	0/8	0/8	0/8
Pair-Fed	0/8	0/8	0/8	0/8	1/8

Table 2
Number of Male Rats Displaying Individual Withdrawal Symptoms as a Function of Exercise and Feeding Conditions

	Teeth Chattering	Ptosis	Abnormal Postures	Wet Dog Shakes	Escape Attempts
Active + 1 hour food intake	8/8	5/8	5/8	1/8	0/8
Active + ad libitum food intake	8/8	0/8	3/8	2/8	0/8
Inactive + 1 hour food intake	5/8	0/8	0/8	0/8	1/8
Inactive + ad libitum food intake restricted	3/8	0/8	0/8	0/8	0/8
	6/8	0/8	0/8	0/8	0/8