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Running and Addiction: Precipitated Withdrawal in a Rat Model of Activity-Based Anorexia

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Exercise improves cardiovascular health, strengthens muscles and bones, stimulates neuroplasticity, and promotes feelings of well-being. However, when taken to extremes, exercise can develop into an addictive-like behavior. To assess the addictive potential of exercise, withdrawal symptoms following injections of 1.0 mg/kg naloxone were compared in active and inactive male and female rats. Active and inactive rats were given food for 1 hr or 24 hr/day. Additionally, a group of inactive rats was pair-fed the amount of food consumed on the previous day by food-restricted active rats. Rats fed for 1 hr/day decreased food intake and lost weight. Additionally, food-restricted active rats increased wheel running. There was a direct relationship between the intensity of running and the severity of withdrawal symptoms. Active food-restricted rats displayed the most withdrawal symptoms, followed by active rats given 24-hr access to food. 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

Physical activity facilitates weight control, improves cardiovascular health, strengthens muscles and bones, promotes neuroplasticity, decreases anxiety, offsets depression, and elevates mood (Brene et al., 2006; Churchill et al., 2002; Greenwood & Fleshner, 2008; Paluska & Schwenk, 2000; Smits et al., 2008; Teychenne, Ball, & Salmon, 2008). However, despite these beneficial outcomes, when taken to extremes, physical activity can develop into an addictivelike behavior. Committed runners appear to be particularly susceptible to the addictive properties of exercise. Runners often report (a) a feeling of euphoria after a strenuous bout of exercise (runner's high), (b) the need to increase the distance run to achieve feelings of well-being (tolerance), (c) difficulties in job performance and social interactions (addiction), and (d) 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 et al., 2008; Smith & Zigmond, 2003). However, as in nonhuman animals, in our own species, physical activity can transition into an addictivelike 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 hr/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 rats display a dramatic increase in wheel running, accompanied by continued reductions in food intake and body weight. Within 7 to 10 days, rats maintained on this schedule die of starvation (Boakes & Dwyer, 1997; Boakes, Mills, & Single, 1999; Kanarek & Collier, 1983; Routtenberg & 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), ABA has been proposed as an animal model of the disease (Aravich, Rieg, Lauterio, & Doerries, 1993; Casper, Sullivan, & Tecott, 2008; Hebebrand et al., 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 (Ferreira et al., 2006; Kanarek, Gerstein, Wildman, Mathes, & D'Anci, 1998; Ozburn, Harris, & Blednov, 2008; Werme, Thoren, Olson, & Brene, 2000). 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 et al., 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 et al., 1998; Mathes & Kanarek, 2006, 2007; Smith & Lyle, 2006; Smith &

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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, 2002). 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. Because 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 & Yancey, 2003), withdrawal symptoms should be particularly evident when rats have experienced a rapid and pronounced increase in running wheel activity, such as that observed with the ABA procedure. To evaluate the addictive properties of running, we injected active and inactive male and female rats with the opioid antagonist naloxone and observed them 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 active rats fed ad libitum.

Experiment 1

Method

Rats, housing and dietary conditions. Forty-four female Long–Evans rats (Charles River Laboratories, Raleigh NC), 8 weeks of age and weighing between 150 and 175 g at the beginning of the experiment, were housed in a temperature-controlled room (21 °C ± 2 °C) maintained on a 12:12 reverse light–dark cycle (lights on at 2000). 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 ($n = 20$) were housed in Wahmann LC34 activity wheels (circumference, 1.13 m) with adjoining cages. Wheel turns were measured with a microswitch so 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).

After 7 days of acclimation to the housing conditions, food restriction was initiated. Ten active and 8 inactive rats were given food for only 1 hr/day (1300–1400), whereas 10 active and 8 inactive rats continued to receive food for 24 hr/day. A fifth group of 8 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, we tested inactive rats tht were given food for 1 hr/day or for 24 hr/day and active rats that were given food for 24 hr/day at the same time. To allow for the same duration of exposure to food restriction, we tested inactive pair-fed rats on the following day.

To precipitate withdrawal, we injected rats subcutaneously with 1.0 mg/kg naloxone HCl (Sigma-Aldrich Corp., St. Louis, MO) and then placed them in a novel Plexiglas observation chamber (60 cm × 30 cm × 25 cm). Rats were observed for 1 hr for signs of withdrawal by two independent observers who were unaware of 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, Nock, & Meyer (2002). Body weights were measured preceding and 30 and 60 min 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; 3–4 shakes = 3; 4 or more shakes = 4), and escape attempts (2–4 attempts = 1, 5–9 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 after 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 with SPSS 15.0 for Windows. We analyzed food intake, wheel turns, and total withdrawal scores either using either independent *t* tests with activity as a between-groups measure or using analyses of variance (ANOVAs) with activity/feeding conditions as between-group measures. We used repeated measures analyses to determine changes in running wheel activity across time. Post hoc comparisons were made using Tukey's least significant difference test. Additionally, we analyzed the withdrawal scores using a nonparametric 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 before 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 rats 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 hr/day (see Figure 1A).

Food intake, body weight, and wheel revolutions after the initiation of food restriction. When given food for only 1 hr/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 that were 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, $F(3, 12) = 3.56$, $p < .05$, during this period, food-restricted active rats ran more than unrestricted active rats. It should be noted that, after rats reached criterion and were tested for naloxone-precipitated withdrawal, they were removed from the wheels and given ad libitum access to food. As rats 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 (see Figure 1B).

Withdrawal scores. Total withdrawal scores after injection of 1.0 mg/kg sc naloxone varied significantly as a function of activity and feeding condition, $F(4, 39) = 15.53$, $p < .001$. 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, ps $< .001$; (see Figure 2). As withdrawal scores can also be interpreted using a ranking system, further analysis using a nonparametric Kruskal–Wallis test showed that withdrawal scores varied significantly, with rats in the active food-restriction condition showing the highest overall withdrawal scores, $\chi^2(4) = 21.82$, $p < .001$.

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 ($r = .453$, $p < .05$). 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 ($r = .655$, $p < .05$) but not for ad libitum-fed rats ($r = .237$, *ns*).

To further evaluate withdrawal, we deteremined the number of rats in a group displaying each withdrawal symptom (see Table 1).

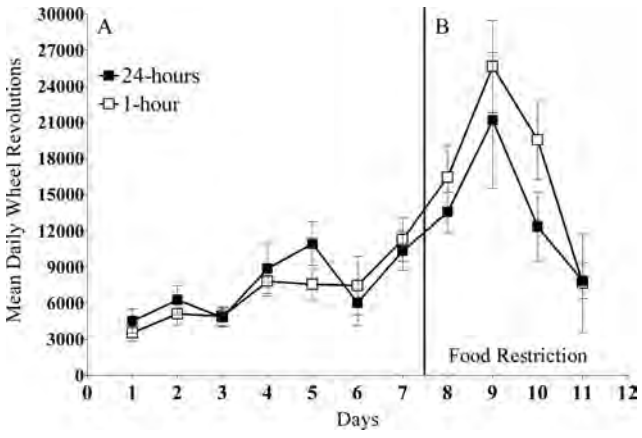


Figure 1. Mean daily number of wheel revolutions preceding food restriction (A) and during food restriction (B) in female rats given food for 24 hr or 1 hr/day.

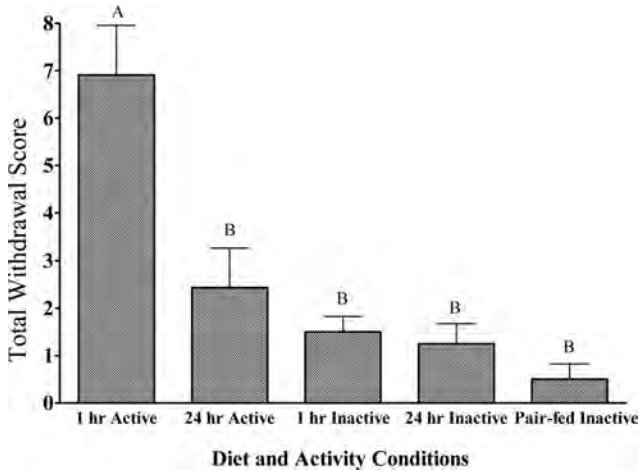


Figure 2. Total withdrawal scores after injections of 1.0 mg/kg sc naloxone in active and inactive female rats given food for 24 hr or 1 hr/day or inactive female rats pair-fed to active–food-restricted female rats. Withdrawal scores not sharing a common letter are significantly different from each other.

Kruskal–Wallis tests showed that there was a significant difference in the number of rats showing teeth chattering, $\chi^2(4) = 13.72$, $p < .01$; ptosis, $\chi^2(4) = 12.78$, $p < .05$; wet-dog shakes, $\chi^2(4) = 13.57$, $p < .01$; and escape attempts, $\chi^2(4) = 16.58$, $p < .005$; with a greater number of active food-restricted rats displaying each symptom than rats in the other groups. There was a trend for abnormal posture to differ with activity condition, $\chi^2(4) = 8.15$, $p < .086$. No other symptoms of withdrawal were observed in any of the groups of rats.

Experiment 2

In Experiment 2, we 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 et al., 2002). Therefore, to allow for the stabilization of wheel running, we gave male rats 25 days to adapt to the wheels before instituting food restriction. Additionally, as male rats typically run less than females (Boakes et al., 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

Rats, housing and dietary conditions. Forty male Long–Evans rats (Charles River Laboratories, Raleigh, NC), 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.

Table 1
No. of Female Rats Displaying Individual Withdrawal Symptoms as a Function of Exercise and Feeding Conditions

Condition	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

To allow for daily wheel turns to reach stable values, we gave all rats 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. Rats then were divided into five groups as described in Experiment 1. Eight active and 8 inactive rats continued to receive unrestricted access to food, whereas 8 active and 8 inactive rats were given food for only 1 hr/day (1300–1400). The final 8 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 test on the subsequent day.

Results

Food intake, body weight, and wheel turns before the initiation of food restriction. Across the 25-day adaptation period, inactive rats consumed significantly ($p < .01$) 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 rats = 355.1 ± 7.0 g; inactive rats = 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), $t(38) = -4.47$, $p < .001$.

During the 25-day adaptation period, mean daily wheel turns increased significantly as a function of time, $F(9, 54) = 11.96$, $p < .001$. However, before food restriction, wheel turns did not differ between active rats that subsequently were given food for 1 hr or 24 hr/day (see Figure 3A).

Food intake, body weight, and wheel turns after the initiation of food restriction. When given food for only 1 hr/day, both active and inactive rats decreased food intake and lost weight (see Figures 4 and 5). There were no differences in food intake between active and inactive rats given food for 24 hr/day. After the initiation of food restriction, the mean daily number of wheel turns for food-restricted rats increased, whereas the number of wheel turns for nonrestricted rats did not (see Figure 3B). Mean daily wheel turns for food-restricted active rats were significantly greater than those of ad libitum-fed rats on Days 2, 3, and 4 after food restriction ($ps < .05$). After rats reached 80% of their prerestriction weight and were tested for naloxone-precipitated withdrawal, they were removed from the wheels and given food ad libitum. As rats that 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 after injection of 1.0 mg/kg sc naloxone varied significantly as a function of activity and feeding condition, $F(4, 39) = 7.71$, $p < .001$. 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, $ps < .001$ (see Figure 6). Moreover, withdrawal scores of active rats given food for 24 hr/day were significantly greater than those of rats in the three inactive conditions ($ps < .05$).

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 nonparametric Kruskal–Wallis test showed that withdrawal scores varied significantly, with rats in the active food-restriction condition showing the highest overall withdrawal scores, $\chi^2(4) = 19.16$, $p < .001$.

The number of rats in a group displaying each withdrawal symptom is shown in Table 2. Kruskal–Wallis tests showed that

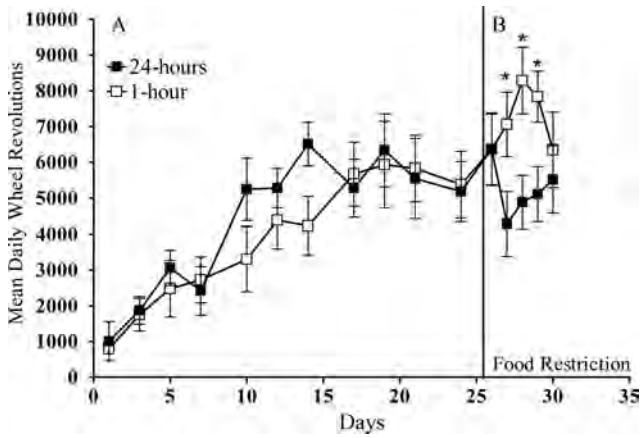


Figure 3. Mean daily number of wheel revolutions preceding food restriction (A) and during food restriction (B) in male rats given food for 24 hr or 1 hr/day.

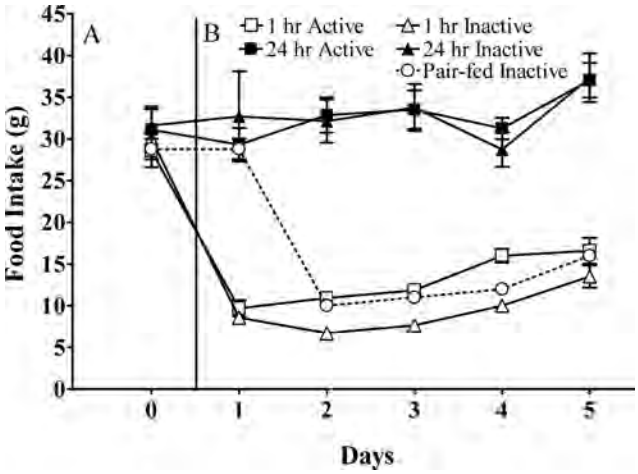


Figure 4. Mean daily food intake on the day preceding food restriction (A) and during food restriction (B) in active and inactive male rats given food for 24 hr or 1 hr/day or inactive male rats pair-fed to active food-restricted male rats.

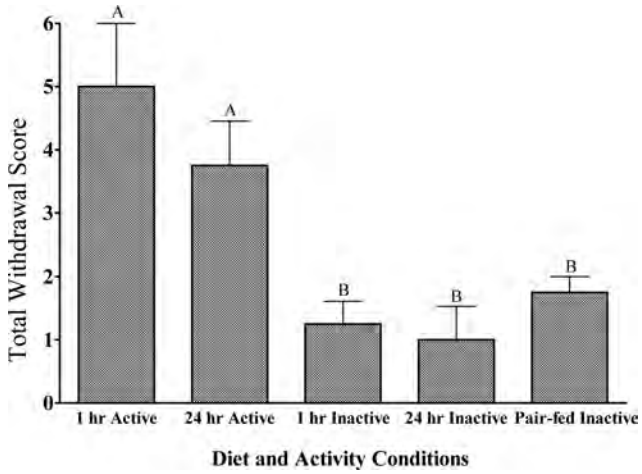


Figure 6. Total withdrawal scores after injections of 1.0 mg/kg sc naloxone in active and inactive male rats given food for 24 hr or 1 hr/day or inactive male rats pair-fed to active food-restricted female rats. Withdrawal scores not sharing a common letter are significantly different from each other.

there was a significant difference in the number of rats in a group showing teeth chattering, $\chi^2(4) = 11.7$, $p < .05$; ptosis, $\chi^2(4) = 21.65$, $p < .001$; and abnormal postures, $\chi^2(4) = 20.13$, $p < .001$; 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.

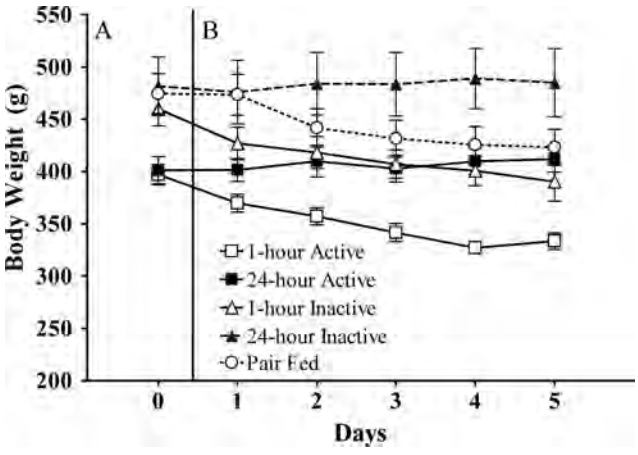


Figure 5. Mean daily body weight on the day preceding food restriction (A) and during food restriction (B) in active and inactive male rats given food for 24 hr or 1 hr/day or inactive male rats pair-fed to active food-restricted male rats.

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 et al., 1999; Hirsch et al., 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. On receiving access to the wheels, female rats made approximately 4,000 wheel turns per day, whereas males averaged only 1,000 wheel turns per day. With time, wheel running increased in both males and females. Specific comparisons between maximum levels of wheel running in nonfood-restricted males and females cannot be made because females ran for only 7 days preceding food restriction, whereas males ran for 25 days. However, by Day 7, females were averaging 13,000 wheel revolutions per day, whereas males were averaging only 5,500 wheel revolutions. During the initial days of food restriction, females increased running to approximately 24,000 wheel revolutions per day, whereas males increased to 9,000 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 cannot be determined whether 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

Table 2
No. of Male Rats Displaying Individual Withdrawal Symptoms as a Function of Exercise and Feeding Conditions

Condition	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

weighed less than ad libitum-fed active rats. 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. However, 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 need to use a group of inactive rats whose body weight is paired to that of active food-restricted rats.

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, 2006; Mathes & Kanarek, 2007; 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 & Kanarek, unpublished data, 2002). 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 that 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 that have been observed between the intensity of aerobic activity and the release of endogenous opioid peptides (Goldfarb, Hatfield, Armstrong, & Potts, 1990; Goldfarb, Jumurtas, Kamimori, Hegde, Ottersletter, & Brown, 1998).

Similarities between the effects of exercise and drugs of abuse extend beyond opiate drugs. Research demonstrating that rats 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, Hunter, & Carroll, 2002; Kanarek, Marks-Kaufman, D'Anci, & Przypek, 1995; McLachlan, Hay, & Coleman, 1994; McMillan, 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 et al., 2007; Smith, Schmidt, Iordanou, & Mustroph, 2007; Werme et al., 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 et al., 2008: Smith et al., 2008). Additionally, like drugs of abuse, running wheel activity increases levels of ΔFosB within the nucleus accumbens, whereas overexpression of ΔFosB in striatal dynorphin neurons enhances both running and drug self-administration (Werme et al., 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 et al., 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 it 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; Franco et al., 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. After naloxone injections, drug-naïve food-restricted active rats displayed symptoms of withdrawal similar to those observed in rats addicted to morphine. 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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