

Experimental and Clinical Psychopharmacology

Naloxone and Rimonabant Reduce the Reinforcing Properties of Exercise in Rats

Erin B. Rasmussen and Conrad Hillman

Online First Publication, June 27, 2011. doi: 10.1037/a0024142

CITATION

Rasmussen, E. B., & Hillman, C. (2011, June 27). Naloxone and Rimonabant Reduce the Reinforcing Properties of Exercise in Rats. *Experimental and Clinical Psychopharmacology*. Advance online publication. doi: 10.1037/a0024142

Naloxone and Rimonabant Reduce the Reinforcing Properties of Exercise in Rats

Erin B. Rasmussen and Conrad Hillman
Idaho State University

Naloxone and rimonabant block neurotransmitter action of some drugs of abuse (such as ethanol, opiates, and nicotine), and thereby reduce drug seeking and self-administration by suppressing the drugs' reinforcing properties. The present study represents an attempt to elucidate whether these drugs may also reduce rewarding properties of other events, in this case, activity-based reinforcement. In Experiment 1, 10 obese and 10 lean Zucker rats pressed a locked door under a progressive ratio schedule of reinforcement that, when unlocked, provided access to a running wheel for 2-min intervals. After baseline breakpoints were established, doses of naloxone (0.3–10 mg/kg) were administered prior to experimental sessions. Obese rats exhibited lower baseline breakpoints for wheel activity, lower response rates, and fewer revolutions compared to lean rats. Naloxone decreased revolutions and response rates for lean and obese rats, but did not reduce breakpoints. In Experiment 2, five Long-Evans rats pressed a door to unlock a wheel for 20 s of wheel activity. Doses of rimonabant (1–10 mg/kg) were administered before some experimental sessions. The highest dose of rimonabant suppressed breakpoints and response rates, but did not affect revolutions. These data suggest that both drugs reduce the reinforcing properties of wheel running, but do so in different manners: naloxone may suppress wheel-based activity (consummatory behavior), but not seeking (appetitive behavior), and rimonabant does the converse. The data also support the role of endocannabinoids in the reinforcing properties of exercise, an implication that is important in terms of CB1 antagonists as a type of pharmacotherapy.

Keywords: exercise, naloxone, obese Zucker, rimonabant, wheel running reinforcement

Antagonist-based pharmacotherapies have attracted attention as treatments that increase the initiation and maintenance of drug abstinence (Cooper & Comer, 2009; Ross & Peselow, 2009). These drugs function by directly or indirectly blocking neurotransmission of dopamine in the mesolimbic reward pathways in the brain, reducing self-administration of drugs of abuse by suppressing the reinforcing or subjective properties of the drug (e.g., Beardsley, Thomas, & McMahon, 2009; Ross & Peslow, 2009). Two such classes of antagonists are opioid blockers and more recently, cannabinoid blockers.

Opioid blockers, such as naloxone and naltrexone, are antagonists of the endogenous opioid neurotransmitter system, which is an established mechanism in alcohol and opioid reward (Herz, 1997; Walker & Koob, 2008). When administered, drinking decreases in alcohol-dependent and heavy drinking populations (e.g., Batki et al., 2007; David-

son, Palfai, Bird, & Swift, 1999; Galloway, Koch, Cello, & Smith, 2005) and heroin use lessons in opioid-dependent individuals (e.g., Sullivan, Vosburg, & Comer, 2006). Animal studies also support that naltrexone and naloxone reduce ethanol self-administration in rodents and primates (e.g., Carroll, Cosgrove, Campbell, Morgan, & Mickelberg, 2000; Escher & Mittleman, 2006; Kamdar et al., 2007; Samson & Doyle, 1985; Schwartz-Stevens, Files, & Samson, 1992; Sharpe & Samson, 2001; Williams & Broadbridge, 2009).

Drugs that antagonize endocannabinoid activity in the brain by blocking the CB1 receptor have drawn recent attention also as a potential pharmacotherapy for putative addictive behaviors (see Beardsley et al., 2009, and Le Foll & Goldberg, 2005, for reviews), especially for nicotine dependence (Beardsley & Thomas, 2005; Beardsley et al., 2009; Cohen, Kudas, & Griebel, 2005; Le Foll, Forget, Aubin, & Goldberg, 2008). This application comes from animal studies that support that pretreatment of rimonabant reduces nicotine self-administration in rats (Cohen, Perrault, Voltz, Steinberg, & Soubrie, 2002) and interferes with conditioned cues associated with the reinstatement of nicotine self-administration (Cohen, Perrault, Griebel, & Soubrie, 2005; Kudas, Cohen, Louis, & Griebel, 2007).

Despite the effectiveness of these antagonists in reducing drug self-administration, there are some drawbacks to their use. Rimonabant, for example, when used to treat obesity (as a substance that blocks food reward) may be associated with an elevated risk of side effects that include major

Erin B. Rasmussen and Conrad Hillman, Department of Psychology, Idaho State University.

This research was supported by a grant from the WeLEAD project that was funded by the National Science Foundation Grant SBE-0620073. We thank Shilo Smith, Jessica Buckley, Mathew Luras, and Jennifer White for assistance with data collection.

Correspondence concerning this article should be addressed to Erin B. Rasmussen, Department of Psychology, Mail Stop 8112, Pocatello, ID 83209-8112. E-mail: rasmerin@isu.edu

depressive symptoms, including suicidal ideation (see, e.g., Scheen, Hollander, Jensen, & Van Gaal, 2006). These side effects (to date) have prevented its acceptance and use by the United States Food and Drug Administration (U.S. FDA, 2007) as a treatment for obesity, and led to its removal in Europe (European Medicines Agency, 2008) until risk potential is better understood.

One manner in which rimonabant's depression-related side effects may be better understood is to conceptualize depression as a condition in which a variety of situations or activities are no longer rewarding (see Costello, 1972). In addition to attenuating the properties of drug reinforcers, rimonabant also reduces the rewarding properties of food (Rasmussen & Huskinson, 2008; Solinas & Goldberg, 2005), the reward efficacy of medial forebrain stimulation (Pillolla et al., 2007; Vlachou, Nomikos, & Panagis, 2006), and some conditioned reinforcers (De Vries & Schoffelmeier, 2005; Rasmussen & Huskinson, 2008). This reduction of behavioral sensitivity to a variety of nondrug reinforcers may be associated with the aforementioned increase in risk of rimonabant-related depression.

Naloxone may also reduce the rewarding properties of a variety of reinforcers besides drugs. For instance, the reward efficacy of standard food pellets (Glass, O'Hare, Cleary, Billington, & Levine, 1999), sweetened condensed milk (Schneider, Heise, & Spanagel, 2000), sucrose (Agustín-Pavón, Martínez-Ricós, Martínez-García, & Lanuza, 1989; Glass et al., 1999), and nucleus accumbens-based brain self stimulation (Trujillo, Belluzzi, & Stein, 1989a; Trujillo, Belluzzi, & Stein, 1989b) diminishes with naloxone administration. There are difficulties with compliance when naloxone is used solely as a pharmacotherapy (see Mark, Kranzler, & Song, 2003); while many factors are implicated as reasons for noncompliance, one may be anhedonia (Zurita, Martijena, Cuadra, Brandão, & Molina, 2010).

An underlying assumption of successful treatment of drug abuse is that individuals must make contact with alternative nondrug reinforcers (see, e.g., reviews on contingency management: Higgins, Heil, & Lussier, 2004; Stitzer & Petry, 2006). If the effectiveness of nondrug reinforcers is reduced by a pharmacotherapy, especially those that are important for maintaining a healthy, drug-free lifestyle, the probability of relapse may increase.

One example of a nondrug reinforcer that has been suggested to be of utility in terms of enhancing abstinence is physical activity. Exercise has been shown to be an effective adjunctive intervention for substance abusers who undergo contingency management (CM) treatment, in that individuals who consistently exercised during the intervention had more sustained periods of abstinence than those who did not (Weinstock, Barry, & Petry, 2008). In other studies, substance abusers who engaged in exercise as a sole treatment for substance abuse exhibited better substance use-related outcomes compared to those not engaging in activity-based treatment (Brown et al., 2009; Brown et al., 2010). Research on exercise as an adjunctive treatment for nicotine dependence also suggests that exercise increases abstinence rates

of nicotine users (Prochaska, Hall, Muñoz, Reus, & Hu, 2008) and improves mood in abstaining smokers (Everson, Daley, & Ussher, 2008).

The present study seeks to characterize antagonist-related effects using a model of wheel-running exercise reinforcement in rats. Wheel running is an ecologically valid model of activity-based reinforcement. Lever pressing for access to a running wheel has been placed under various schedules of reinforcement, and schedule patterning that is similar to that generated by other reinforcers such as food, water, and sucrose has been demonstrated (Belke, 1996, 2004; Belke, Pierce & Jensen, 2004; Collier & Hirsch, 1971; Iversen, 1993; Kagan & Brekun, 1953). Wheel activity has also been placed under a progressive ratio (PR) schedule of reinforcement (Pierce, Epling, & Boer, 1986; Smith & Rasmussen, 2010). The PR schedule is a well-established procedure that determines a reinforcer's value by increasing the response requirement for access to it within session (see Markou et al., 1993; Stafford, LeSage, & Glowa, 1998 for reviews). The point at which ratio strain occurs is referred to as the breakpoint and is used as a measure of the reinforcer's value. The PR schedule also allows for differentiation of specific motivational effects of behavior to be isolated. First, there are behavioral endpoints (e.g., breakpoint) involved with gaining access to the reinforcer, that is, seeking (appetitive behavior). Second, other features of behavior allow examination of consuming or engaging in the reinforcer, that is, consummatory behavior. Wheel revolutions made during the reinforcer interval would be an example.

Under the PR schedule, rats have been shown to exhibit reasonably high breakpoints (e.g., 100 responses) for 60-s (Pierce et al., 1986) and 120-s (Smith & Rasmussen, 2010) access to a running wheel. However, to date there are few, if any, pharmacological studies that have examined how antagonist-based drugs influence motivational properties of wheel activity reinforcement, which could have implications for side effects of the drugs. The present study examines the effects of naloxone and rimonabant on wheel running reinforcement.

Experiment 1

Methods

Subjects. Ten female obese *fa/fa* Zucker rats and 10 female lean (*Fa/fa* or *Fa/Fa*) Zucker rats (approximately 4–6 weeks old) were purchased from a commercial breeder (Harlan, Livermore, CA). Female rats were used in this study because they often exhibit higher rates of free wheel running when compared to males (e.g., Eikelboom & Mills, 1988; Schull, Walker, Fitzgerald, & Hilivirta, 1989; Tokuyama, Saito, & Okuda, 1982). Rats from the Zucker strain were used because obese Zuckers exhibit lower sensitivity to wheel reinforcement compared to leans (Smith & Rasmussen, 2010). This difference provided an opportunity to determine if naloxone would work similarly on behavior of rats that had differing motivations for wheel reinforcement, and to determine if their genotype would manifest in different sensitivities to naloxone.

Rats were singly housed in clear, Plexiglas home cages and maintained in a temperature- and humidity-controlled room (approximately 72°F) under a 12-hr light/dark cycle. One obese Zucker rat developed skin lesions during the course of the study and after unsuccessful treatment was euthanized. This rat did not complete a drug profile for the 10 mg/kg dose of naloxone. Half of the rats in each group received acute administrations of 2-AG, a natural cannabinoid ligand, at least two weeks prior to baseline data collection (and at least four weeks prior to naloxone administrations). This washout period allowed sufficient time for the 2-AG to have left the system before the present experiment began. In addition, data from these rats were analyzed and found to be statistically indistinguishable from rats that did not receive 2-AG (all p 's > 0.4), so their data were pooled. At the time of testing, the leans weighed 211.63 g ($SEM = 3.22$) and the obese weighed 437.96 g ($SEM = 10.58$) and this difference was statistically significant $t(10.65) = -20.47$, $p < .01$ (Levene correction for unequal variances).

Animals were given ad libitum access to water when not in experimental sessions. Animals also were given free access to food for 2 hr immediately following each operant session, which is a procedure that consistently allows lean and obese Zucker rats to eat about 2.3% of their body weights. This procedure holds food deprivation constant, but allows slow growth across the life span, which allows expression of the obese and lean phenotypes (Rasmussen & Huskinson, 2008; Rasmussen, Reilly, & Hillman, 2010; Smith & Rasmussen, 2010).

Apparatus. Five Coulbourn activity wheels (9 × 8 × 3.5 in) were each attached to five standard two-lever operant chambers. Access to the wheel from the chamber was possible through a swinging door. During an experimental session, this door was locked, but would unlock under behavioral contingencies that are specified in the procedures. Each wheel and chamber was enclosed in a sound-attenuating box. White noise was used during all operant sessions to mask any external stimuli. A Windows-based computer with Graphic State software was used to collect data and control experimental contingencies.

Drug. Naloxone hydrochloride (0.3–10 mg/kg) was purchased from Sigma-Aldrich. It was dissolved in a saline vehicle (1 mg/ml volume).

Procedure

Wheel reinforcement training. Specific procedures are described elsewhere (Smith & Rasmussen, 2010), but will be summarized here. Each rat was placed inside an operant chamber at the beginning of a session. Rats were required to press the locked swinging door under a FR5 schedule of wheel reinforcement, in which five door-presses on the locked door led to the door unlocking and allowed access to the running wheel for a 2-min period. After the 2 min elapsed, the wheel locked and the swinging door remained unlocked, such that the rat could access the chamber again. Once the rat moved to the chamber, the door locked and was therefore ready for the next ratio. Sessions were 60 min long

and individual sessions were run daily at the same time in the afternoon (± 30 min) until a rat demonstrated stability (defined as three consecutive sessions in which the number of reinforcers earned did not deviate by more than 10% and there were no visible trends). Similar numbers of lean and obese rats (e.g., two lean and three obese, and vice versa) were run within each session, so specific time of day within the afternoon was counterbalanced across group.

Progressive ratio schedule. After the rats were lever-press trained, door-pressing was placed under a progressive ratio schedule of wheel reinforcement (PR) in which the response requirement for 2-min access to the wheel started at five door presses and increased in a systematic fashion within the session with each earned reinforcer. Similar to Smith and Rasmussen (2010), the response requirements for the progressive ratio schedule were: 5, 15, 30, 50, 90, and 150. Each session ended when ratio strain occurred (defined as a ratio not being completed within 20 consecutive min). Sessions were conducted on Sundays through Fridays. Half of the rats completed baseline PR sessions on Mondays, Wednesdays, and Fridays; half completed them Sundays, Tuesdays, and Thursdays. FR1 sessions, in which a single door press resulted in access to the running wheel for 2 min, were in effect on days between PR sessions in order to maintain the door-press. This maintenance schedule has been used in other studies (Smith & Rasmussen, 2010; Solinas & Goldberg, 2005; Wakley & Rasmussen, 2009). FR1 sessions ended after five wheel reinforcers were earned.

Naloxone. Once rats showed stability under baseline PR sessions, naloxone administration began. Stability was determined by visual inspection of breakpoints ± 1 PR step across three PR sessions with no trend. (Because FR 1 sessions separated each successive PR session, the three PR days spanned the female rat 4-day estrous cycle, ensuring that the cycle did not confound data.) A single acute injection of naloxone in a 1 ml/kg solution was administered by intraperitoneal injection to a rat 30 min before a session began, to ensure peak absorption when the experimental session began. Administrations began with the smallest dose of the drug and increased in half-log units on subsequent drug sessions (one dose was administered per rat per session). If a dose reduced behavior by greater than 50%, the next dose was not attempted (this occurred with one lean female). Doses were administered on consecutive PR days, so at least two days separated drug administrations. All procedures were approved by the Idaho State University's Institution for Animal Care and Use Committee.

Extinction condition. Once all doses for the assigned drug were completed under PR, an extinction condition took place that was procedurally similar to that described in Smith and Rasmussen (2010). Here, door pressing was identical to the progressive ratio condition, except that the wheel was locked throughout the session. The purpose of the extinction condition was to ensure that door pressing was maintained by wheel activity. Extinction sessions continued until behavior stabilized. After extinction sessions, the 10 mg/kg dose (the dose that caused the greatest behavioral change from baseline) was administered before one final extinction condition (only the 3 mg/kg dose was ad-

ministered to the previously mentioned rat who demonstrated sensitivity to naloxone). This was done to examine whether naloxone's effects were specific to behavior maintained by wheel running, that is, to determine if a drug effect observed under the PR condition required the running wheel reinforcer.

Analysis

Data from the last three stable baseline PR sessions were averaged for each rat and analyzed for breakpoint (last ratio completed before ratio strain ensued), door-press rates (door presses per minute), and wheel revolutions per reinforcer. Door-press rates were determined by dividing the number of door-press responses across the session by the session duration (subtracting out each reinforcer interval). Means (lean vs. obese) for breakpoints, door-press rates, and revolutions per reinforcer (the mean number of revolutions per 2-min reinforcer) were compared across group (obese vs. lean) and naloxone dose using two-way repeated measures analysis of variance (ANOVA). Because lean rats' data were significantly higher than obese rats' data, each rat's datum from the naloxone dose was divided by its baseline datum. This allowed standardization across rats to compare sensitivity to naloxone. These data were also analyzed using a two-way ANOVA with repeated measures to determine main effects of dose, group, and Group \times dose interactions. Post hoc contrasts between specific doses are reported also. Greenhouse-Geisser adjustments to the degrees of freedom are included when sphericity violations occurred.

In repeated measures analyses, only subjects with all of the conditions represented are accepted by SPSS for analysis. Two rats did not receive the 10 mg/kg dose (one because the 3 mg/kg dose reduced behavior to less than 50% of baseline; the other because it died). Therefore we had to conduct analyses in two ways: 1) We conducted them without the rat that was missing the 10 mg/kg dose (highest dose), which dropped the n to 18; and 2) we conducted them with all rats in the analysis, but the 10 mg/kg dose was not included as a within-subjects variable. Excluding the two rats did not change the outcome of any analysis conducted, therefore the reported analyses are those conducted without the two rats.

Data under extinction conditions were analyzed using two-way repeated measures ANOVAs (extinction vs. PR condition as a within-subjects variable and group as a between-subjects variable). Two-way repeated measures ANOVAs also compared data under vehicle versus the dose of naloxone that caused the greatest change from placebo (in most cases 10 mg/kg) and group for PR and extinction conditions. Data from the last extinction session for each rat was used in the analysis, in order to demonstrate the reduction in behavior.

Results

There were no group differences in acquisition of the lever press. Figure 1 shows that naloxone dose-dependently

decreased revolutions per reinforcer $F(3.09, 49.38) = 6.17$, $p < .01$, $\eta_p^2 = 0.28$; G-G correction. There was a significant main effect of group $F(1, 16) = 52.62$, $p < .01$, $\eta_p^2 = 0.77$ but no interaction. Post hoc contrasts revealed a significant difference in the vehicle versus 10 mg/kg dose $F(1, 16) = 16.39$, $p < .01$, $\eta_p^2 = 0.51$. When presented as percent of baseline (top right), naloxone dose-dependently decreased the number of revolutions emitted per reinforcer $F(3.23, 51.6) = 5.72$, $p < .01$, $\eta_p^2 = 0.27$, however, there was no main effect of group nor a significant interaction. Post hoc contrasts again showed a significant difference between vehicle and the 10 mg/kg dose $F(1, 16) = 19.91$, $p < 0.01$, $\eta_p^2 = 0.55$.

Naloxone significantly reduced response rate $F(2.60, 41.63) = 3.19$, $p = .01$, $\eta_p^2 = 0.17$. Obese rats had significantly lower rates than leans $F(1, 16) = 21.71$, $p < .01$, $\eta_p^2 = 0.46$, but there was no Group \times Dose interaction. Post hoc contrasts revealed significant differences between the vehicle dose and the 1 mg/kg and 10 mg/kg doses $F(1, 16) = 5.56$, $p = 0.03$, $\eta_p^2 = 0.26$; $F(1, 16) = 4.49$, $p = .05$, respectively. The 3 mg/kg dose was marginally different from vehicle $F(1, 16) = 3.71$, $p = .07$. When data were analyzed as percent of baseline, there remained a main effect of dose $F(2.96, 47.32) = 3.52$, $p = .02$, $\eta_p^2 = 0.18$, but there was no main effect of group or an interaction. Post hoc contrasts revealed significant differences between the vehicle and the 1 mg/kg, 3 mg/kg, and 10 mg/kg doses $F(1, 16) = 12.12$, $p < .01$, $\eta_p^2 = 0.43$; $F(1, 16) = 5.9$, $p = .03$, $\eta_p^2 = 0.27$; $F(1, 16) = 5.48$, $p = .03$, $\eta_p^2 = 0.26$, respectively.

Naloxone did not affect breakpoints for obese and lean rats, though, there was a significant main effect of group $F(1, 16) = 14.38$, $p < .01$, $\eta_p^2 = 0.47$, but no interaction. When data were represented as percent of baseline (top right), there was not a significant main effect of dose, group, nor a dose \times Group interaction.

Figure 2 shows extinction (EXT) significantly reduced breakpoints compared to baseline PR conditions (EXT $M = 26.0$; $SEM = 3.56$ for leans and $M = 19.44$; $SEM = 3.58$ for obese) $F(1, 18) = 70.16$, $p < .01$, $\eta_p^2 = 0.80$. There was also a main effect of group $F(1, 18) = 5.10$, $p = .04$; $\eta_p^2 = 0.22$, and a significant interaction between group and extinction $F(1, 18) = 9.82$, $p < .01$; $\eta_p^2 = 0.35$. The highest dose of naloxone (EXT/NAL) significantly increased breakpoints under extinction to 52 ($SEM = 6.96$) for the lean rats, and 38.50 ($SEM = 8.40$) for obese rats $F(1, 18) = 16.82$, $p < 0.01$, $\eta_p^2 = 0.48$. There was also a main effect of group $F(1, 18) = 5.48$, $p = .03$, $\eta_p^2 = 0.23$ and an interaction $F(1, 18) = 4.38$, $p = .05$, $\eta_p^2 = 0.20$.

Obese and leans rats' breakpoints under vehicle were similar to baseline. The highest dose of naloxone (PR/NAL) did not significantly affect breakpoints for either group. Extinction (EXT) significantly reduced means for leans to 0.31 ($SEM = 0.03$), and for obese rats to 0.49 ($SEM = 0.08$) of baseline $F(1, 18) = 21.73$, $p < .01$, $\eta_p^2 = 0.92$. There was a significant main effect for group $F(1, 18) = 4.6$, $p = .05$, $\eta_p^2 = 0.20$ and an interaction $F(1, 18) = 4.6$, $p = .05$, $\eta_p^2 = 0.20$. The highest dose of naloxone

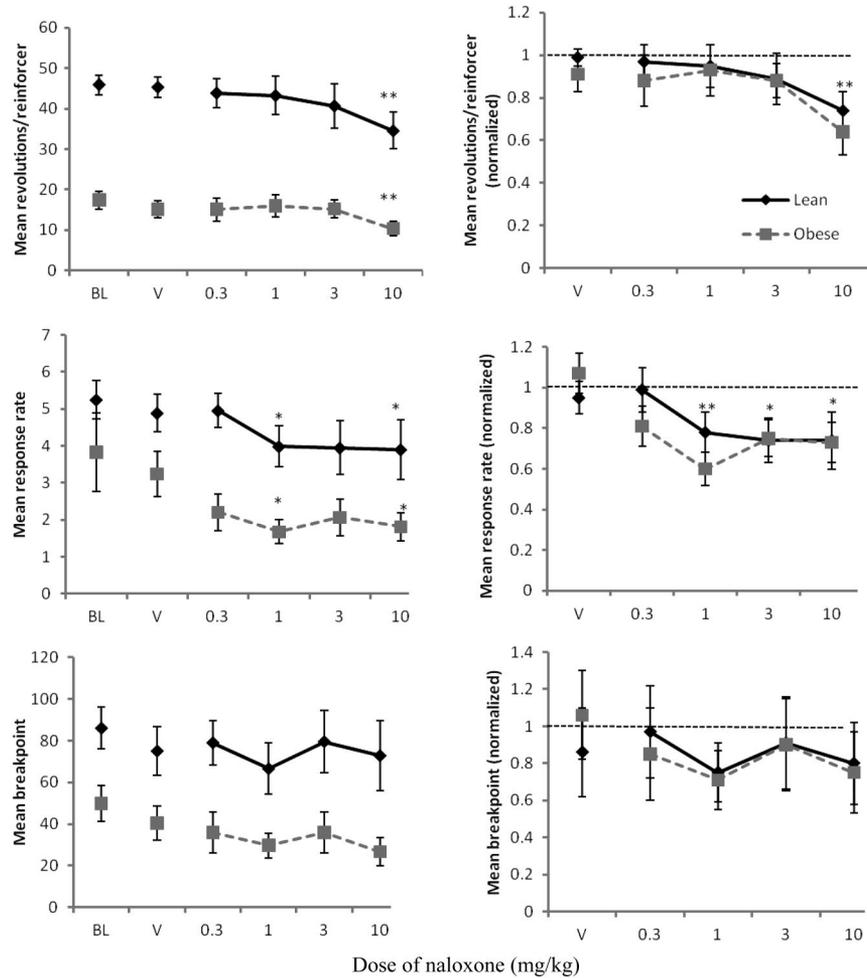


Figure 1. Mean revolutions per reinforcer interval (top), response rate (middle), and breakpoints (bottom) as a function of dose naloxone. The same data are expressed as percent of baseline in the right column. Lean rat (diamonds) and obese (squares) rats are represented. Error bars represent 1 SEM. Dashed horizontal line represents 100% of baseline (no change from baseline). * $p < .05$ compared to vehicle, ** $p < .01$ compared to vehicle.

increased means under extinction compared to the extinction-no drug condition, and this increase was significant $F(1, 18) = 9.64, p < .01, \eta_p^2 = 0.35$. There was no main effect for group or an interaction.

Discussion

The current study was the first, to our knowledge, to examine the effects of naloxone on wheel running as a reinforcer contingent upon a behavioral response in lean and obese Zucker rats. Obese Zucker rats had significantly lower baseline and vehicle breakpoints, response rates, and revolutions per reinforcer than lean rats, suggesting obese rats had overall lower motivation for wheel-based activity than lean rats. In addition, these group differences provided an opportunity to evaluate and compare naloxone's effects on behavior maintained

by wheel-based activity that had low (obese rats) and high (lean rats) reinforcer efficacy.

Naloxone reduced revolutions per reinforcer and doorpress response rate in both groups, though only the highest dose of naloxone was effective at suppressing revolutions. No dose of naloxone increased any of the behavioral measures, suggesting a mono-phasic behavioral effect. Previous studies have examined the effects of acute naloxone on free wheel running, and have found that doses similar to the ones used in the present study reduced wheel running revolutions (Boer, Epling, Pierce, & Russell, 1990; Sisti & Lewis, 2001). Results from these studies have been attributed to a reduction of motivation for running. Because naloxone did not affect breakpoints, it appears that naloxone's effects are specific to the consummatory aspects of wheel running. It may also be the case that naloxone reduces wheel activity

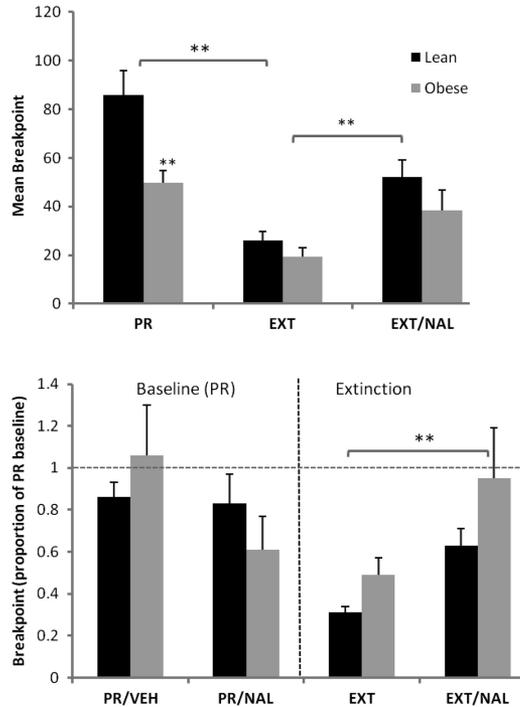


Figure 2. Top: Mean breakpoint as a function of baseline progressive ratio, extinction, extinction with the 10 mg/kg dose of naloxone (EXT/NAL) for lean (dark bars) and obese (light bars) rats. Error bars represent 1 SEM. Bottom: The same data represented as percent of baseline. The dashed horizontal line represents 100% of baseline (no change). ** $p < .01$.

through motor effects, though this is unlikely, as all three dependent variables would have been lower in this circumstance.

When proportion of baseline was analyzed to normalize group differences observed under baseline and vehicle conditions, disparities in drug sensitivity were not revealed. The reductions (percent of baseline) observed at the 10 mg/kg doses were similar across both groups—about a 20–30% decrease from baseline. This suggests that, despite the behavioral and genetic differences in the lean and obese Zucker rats, the two types of rats show a comparable response to opioid blockade with naloxone.

In addition to drugs of abuse, naloxone reduces breakpoints for food under PR schedules of reinforcement (Glass et al., 1999; Solinas & Goldberg, 2005). As such, it was hypothesized that exercise may have been another outcome to which naloxone's reward-reducing effects could be generalized, especially since endogenous opioid peptides are involved in exercise (e.g., Daniel, Martin, & Carter, 1992; Järvekülg & Viru, 2002; Spanagel, Herz, Bals-Kubik, & Shippenberg, 1991). The data, however, suggest that naloxone may affect the consummatory behaviors involved in exercise, but not behaviors involved with seeking exercise. Interestingly, Sharpe and Samson (2001) reported a similar effect with ethanol. In their study, naloxone significantly

decreased alcohol consumption, but did not strongly affect appetitive behaviors related to ethanol seeking (i.e., lever presses).

An extinction condition was used in the present study to determine whether wheel activity was necessary to maintain the door-press response, that is, to ensure that wheel activity was indeed a reinforcer. Extinction reduced breakpoints by 50–75% of the PR condition. Therefore, wheel activity appeared necessary to maintain door pressing. Data from the extinction condition also showed that the highest dose of naloxone significantly increased breakpoints for both groups compared to extinction alone (no drug) condition. These findings suggest that naloxone's effects on activity are complex, and may involve more than one mechanism. It is unclear from these data what that mechanism may be, however, rate dependence may be speculated as an option (see Dews, 1955). Dews first reported that particular doses of pentobarbital had differential effects on behavior, depending on the baseline response rate that was first established. For example, a 1 mg/kg dose of pentobarbital increased response rates when baseline response rates were high; the same dose reduced response rates substantially when baseline response rates were low. While rate dependence has not been reported with naloxone to our knowledge, it may be possible that naloxone affects behavior by this mechanism.

One limitation to the current study involved the PR progression used. With only six values in the progression, we were able to capture between-groups differences in lean and obese rats, but this progression may have limited the chance to observe more subtle effects that may have been associated with the drug's effects on breakpoint. This limitation may be alleviated by using a greater number of values in the progression, but with smaller differences between them. Therefore, in the next experiment we used the Roberts and Bennett (1993) exponential progression, which meets this requirement. Because there was concern that adding values to the PR progression would lead to a greater number of 2-min reinforcers, and therefore longer session durations, which would compromise the collection of data during the duration of a peak drug effect, other adjustments to the PR schedule were made: We reduced the reinforcer duration from 120 s to 20 s and arranged the door-press operandum such that it was manipulated from inside the wheel instead of outside. The latter adjustment would eliminate travel time from the operandum to the wheel.

Experiment 2

Methods

Subjects. Five adult female Long-Evans rats were used and maintained at 90% of free feeding body weight. Females were again selected because they have higher running rates than males (e.g., Eikelboom & Mills, 1988; Tokuyama, Saito, & Okuda, 1982). Similar to Experiment 1, rats were food deprived because slight to moderate food deprivation enhances the reinforcing properties of wheel running and wheel activity (e.g., Connally, 1969; Pierce, Epling, & Boer, 1986). Zuckers were not used in this experiment,

because there were no differences in drug sensitivity to naloxone found between strains (Experiment 1). Because the rats were a standard laboratory strain (i.e., not Zuckers, which requires growth of body mass over time), weights were maintained in a more traditional manner.

Apparatus. The same Coulbourn activity wheels (22.9 cm in diameter; 9 cm wide) were used. In this experiment, the rat was placed in the wheel for the entire session and the door to the chamber remained locked during this time. When the session began, the wheel was locked, such that the rat could not run in the wheel. The door could then be pressed from inside the wheel. Under certain conditions, door presses would unlock the wheel, such that the rat could run for a 20-s interval, then the wheel would lock again. In addition, a light mounted above the activity wheel would illuminate during the wheel reinforcer interval.

Drug. Rimonabant (National Institute of Mental Health Chemical Synthesis and Drug Supply Program), a cannabinoid antagonist/inverse agonist, was dissolved in a 1:1:18 ethanol (Sigma), Cremaphor (Sigma), and saline solution (1 ml/kg) and was administered via intraperitoneal injection 1 hr prior to the start of PR sessions so peak effect of the drug coincided with the beginning of the experimental session. A saline vehicle (1 ml/kg) was administered intraperitoneally prior to the beginning of some progressive ratio sessions.

Procedure

Wheel training. A rat was placed inside the wheel and the swinging door was locked. Similar to Experiment 1, door pressing (though the rat pressed from inside the wheel) was reinforced under an FR5 schedule of reinforcement, except this contingency unlocked the wheel for 20 s. The wheel locked and the light turned off when the reinforcer interval was complete. Sessions ended when 15 reinforcers had been reached or no responding occurred for 15 min.

Progressive ratio. After training, door-pressing were placed under a PR schedule. The Roberts and Bennett (1993) progression was used. Here, the response requirement increased within the experimental session by an exponent of 0.2 multiplied by the number of reinforcers earned in the session to that point and rounded to the nearest integer. It produces the following values: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 98, and 118. Sessions ended when a single ratio was not completed within 15 min. The last earned ratio was considered the rat's breakpoint. Sessions were conducted at the same time Mondays through Fridays (± 10 min) and were conducted in the afternoons (similar to Experiment 1). Rats ran under PR schedules three times per week. Maintenance (FR 5) schedules were run the day following the PR session, similar to Experiment 1.

Rimonabant. After baseline data were collected, vehicle sessions commenced in which acute doses of saline were administered intraperitoneally individually 60 min before a PR session. Once breakpoints stabilized under vehicle conditions, dose-response determinations for rimonabant commenced. A single acute dose of rimonabant (1–10 mg/kg) was administered intraperitoneally 60 min prior to PR ses-

sions (to allow peak absorption to occur during the experimental session), beginning with the smallest dose of the drug. These doses, and the absorption time, were chosen based on other studies that have examined rimonabant's effects on operant behavior (e.g., Rasmussen & Huskinson, 2008; Solinas & Goldberg, 2005; Wakely & Rasmussen, 2009).

Extinction condition with and without light. Once all doses of rimonabant were completed under PR schedules, two extinction conditions took place to ensure the unlocked wheel maintained the door press. The first extinction schedule was identical to a PR schedule, except the wheel remained locked throughout the session. The cue light that was presented when a ratio was complete was still programmed to illuminate. Once behavior stabilized under this condition, a single 10 mg/kg dose of rimonabant was administered before a final session of extinction. After the "extinction with light condition" was complete, the second extinction condition was implemented. Here, the cue light that signaled completion of a ratio was removed. Once behavior stabilized under this condition, a single 10 mg/kg dose of rimonabant was administered before the final session. These extinction conditions allowed rimonabant's effect to be compared not only to behavior maintained by wheel activity, but also to cues that may serve as conditioned reinforcers to wheel activity.

Analysis. Repeated-measures ANOVAs (dose of rimonabant as within-subjects variable) were performed on revolutions per reinforcer interval, breakpoints, and response rate, similar to Experiment 1. Post hoc contrasts are reported.

Results

Figure 3 shows that rimonabant significantly reduced breakpoint $F(4, 16) = 2.8, p = .05, \eta_p^2 = 0.41$, and response rate $F(4, 16) = 5.28, p < .01, \eta_p^2 = 0.57$, but did not affect revolutions. Contrasts revealed that the 10 mg/kg dose significantly reduced breakpoints $F(1, 4) = 4.52, p = .05, \eta_p^2 = 0.58$ and door-pressing rates $F(1, 4) = 6.24, p = .05, \eta_p^2 = 0.61$ compared to vehicle. No dose of rimonabant reduced revolutions per reinforcer interval.

Behavior under extinction did not differ with or without the cue light, so the cue light only condition is shown in Figure 4. Paired-sample t tests confirmed that extinction reduced breakpoints significantly from baseline PR conditions $t(4) = 2.84, p = .05$, but the 10 mg/kg dose did not affect behavior under extinction. Rimonabant also did not affect behavior under extinction under the light-off extinction condition.

Discussion

The 10 mg/kg dose of rimonabant reduced breakpoints for wheel-based activity. In addition, door-pressing response rate was suppressed at this dose. However, wheel revolutions were unaffected by any dose of rimonabant. These data suggest that behaviors involved with wheel

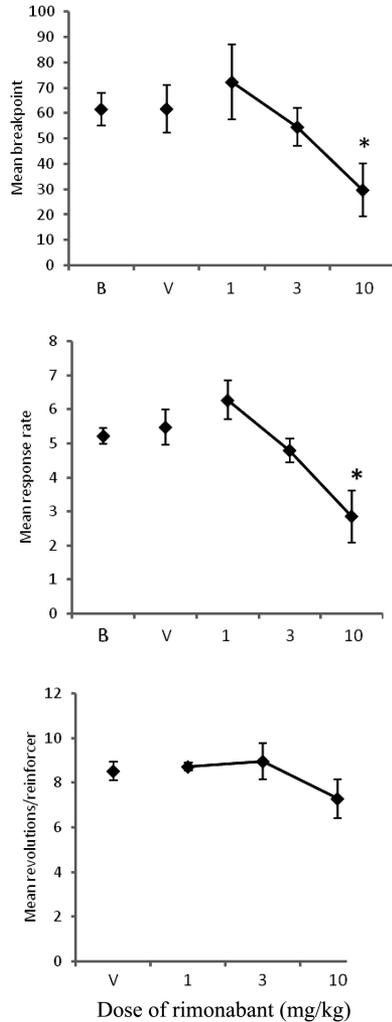


Figure 3. Shows mean breakpoints (top), response rate (middle) and revolutions per reinforcer (bottom) as a function of dose of rimonabant. * $p < .05$.

seeking, but not wheel activity per se, were affected by the highest dose of rimonabant. Importantly, the 10 mg/kg dose of rimonabant has also been associated with at least a 40% decrease in food reinforcer efficacy in other studies using progressive ratio schedules with food reinforcement (see Rasmussen & Huskinson, 2008; Solinas & Goldberg, 2005; Wakley & Rasmussen, 2009).

In the rimonabant experiment, we placed an extinction condition in effect by locking the wheel throughout the session, such that door-presses did not result in a moving wheel. This was conducted to replicate whether door-pressing was maintained by exercise-based reinforcement. This extinction condition was different from Experiment 1, in that the operant was more highly accessible to the rat (since the rat was restricted to the wheel instead of the operant chamber) and therefore had a lower response cost, in terms of making contact with the wheel. In addition, a different strain of rat was used and the parameters of the PR sched-

ules that preceded extinction differed. Nonetheless, when door-pressing did not unlock the wheel, breakpoints decreased by >50%. Rimonabant did not further reduce this decrease when the cue light that signaled completion of a ratio was presented or withheld. This suggests that 1) wheel activity is necessary for rimonabant to affect behavior in this context, and 2) rimonabant does not likely affect cues conditioned to wheel activity. This is noteworthy, as rimonabant has been reported to reduce the reinforcing properties of other types of conditioned reinforcers, for example, cues associated with food (Rasmussen & Huskinson, 2008) and drugs (e.g., Forget, Hamon, & Thiebot, 2005; Forget, Berthelemy, Saurini, Hamon, & Thiebot, 2006).

Keeney et al. (2008) reported rimonabant-induced reductions in free wheel running (i.e., revolutions) in mice that were high-running (HR) and control rats. We did not see rimonabant-related changes in revolutions in this study, though this could be due to the nature of the subjects used (Keeney used mice; the present study used rats) and that a progressive ratio was used that limited access to the running wheel. It was interesting, though, that in the Keeney study, the HR rats exhibited a heightened sensitivity to rimonabant, again implicating the ECB system in running-based activity.

It should be pointed out that the parameters of the PR schedule in Experiment 2 were different from Experiment 1, but yielded values of breakpoint, response rate, and revolutions per reinforcer interval that were similar to Experiment 1. Long-Evans rats produced mean breakpoints for wheel activity that were around 60, which was within the range of the lean and obese rats (50–90). Response rates were similar (around five responses per minute). Revolutions per reinforcer interval in the present experiment were lower, though that may likely be due to a shortened reinforcer interval (20 s vs. 120 s from Experiment 1). If revolutions per reinforcer are divided by the number of seconds in each reinforcer interval for a standardized measure of revolutions per second, however, the lean rats in Experiment 1 had very similar revolutions rates (0.4 revolutions/s) compared to those in Experiment 2 (0.4 rev/s). The obese rats from Experiment 1, however, had lower revolution rates (0.15 rev/s). These data suggest that though

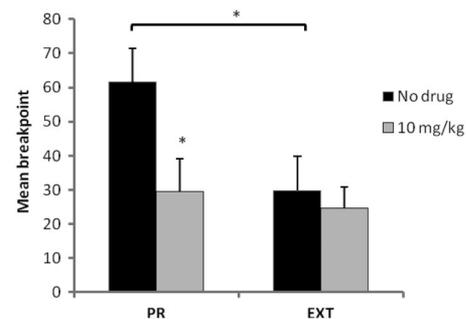


Figure 4. Shows mean breakpoints under PR versus the extinction (cue light) condition under no drug (dark) versus the 10 mg/kg dose of rimonabant (light). * $p < .05$.

parameters of the progressive ratio schedules were different across the two experiments, they produced behavior that was similar across experiments and strains of rats, yielding converging data that each progressive ratio schedule was adequately measuring the reinforcing value of exercise.

Though the present study reports behavioral similarities in the two implementations of the PR schedule, it should be mentioned that Belke and Christie-Fougere (2006) found differences in behavior when wheel reinforcer durations differed. In their study, lever-press pausing under a fixed interval schedule increased as a function of the duration of the wheel reinforcer interval, which varied between 15 and 60 s. Moreover, revolution rates during the reinforcer interval were higher in intervals that were lower in duration. The differences in the results of the present study versus theirs may be related to the schedule that maintained the behavior (the PR schedule vs. the FI schedule). More research on the schedule-controlled nuances of wheel activity as a reinforcer may be required to examine how different parameters of these schedules may influence specific features of behavior.

The data from this experiment may have implications for the rimonabant-related increase in risk of depressive symptoms reported in the Rimonabant in Obesity (RIO) clinical trials studies (Banerji & Tiewala, 2006; Despres, Golav, & Sjostrom, 2005; Pi-Sunyer, Aronne, Heshmati, Devin, & Rosenstock, 2006; Scheen, Finer, Hollander, Jensen, & Van Gaal, 2006). While the vast majority of the participants did not report depressive symptoms over the course of the study, 0–0.09% of the placebo group and 0.06–3% of the 20 mg rimonabant group dropped out due to symptoms of depression, major depression, or depressed mood. The average concentration of rimonabant administered in the RIO studies (calculated by dividing the dose by the reported average body mass in kg) was about 0.10 mg/kg and 4.65 mg/kg for the 5 mg and 20 mg doses, respectively. The 20 mg dose, then, resides within the range of doses used in the present study, which was 1–10 mg/kg. Given that a small portion of this group experienced depressive symptoms, one may speculate that the mechanism may be associated with a sensitivity to the drug that may result in a general suppression of activities that may be viewed as reinforcing (such as exercise). More research on this possible link is suggested.

General Discussion

Experiments 1 and 2 showed that the dose range of two antagonists that block the reinforcing properties of drugs of abuse may also affect the reinforcing properties of exercise, though these antagonists may work in different manners. Naloxone dose dependently reduced wheel revolutions (consummatory behavior) without affecting breakpoints (appetitive behavior) in Zucker rats, and rimonabant affected appetitive, without affecting consummatory, behavior in Long-Evans rats. This study was the first to demonstrate naloxone and rimonabant's effects on contingent access to exercise. These data may provide further support that the opioid system, that is, endogenous opioid peptides, is involved with exercise reward (e.g., Daniel et al., 1992;

Järvekiilg, & Viru, 2002; Spanagel et al., 1991). These data also support other research that suggests that the endocannabinoid system may also be involved in exercise reward (e.g., Dubreucq, Koehl, Abrous, Marsicano, & Chaouloff, 2010; Hill et al., 2010; Smith & Rasmussen, 2010; Sparling, Giuffrida, Piomelli, Roskopf, & Dietrich, 2003). While there is growing evidence that opiate-based reinforcement is modulated through cannabinoid activity and vice versa (e.g., Caille & Parsons, 2006; Kirkham & Williams, 2001; Navarro et al., 2004; Solinas & Goldberg, 2005), it is unclear at this point whether this interaction is implicated in exercise reward.

It should be pointed out that the data generated from this study are limited somewhat by the subjects used. In Experiment 1, half of the subjects in each group had previous exposure to 2-AG. Because the data were indistinguishable in those that had this history, they were grouped together for analysis. In one manner, because the effects were similar across animals with and without this experience, the effects may be said to generalize across rats with a 2-AG history. However, an argument can be made that this history was not held constant within each group and therefore may limit the internal validity of the study. Similarly, in Experiment 2, only five rats' data were used and within-subject rimonabant-related effects were compared. While effect sizes for rimonabant in these data ranged between 0.57–0.61, the number of subjects can be argued to be lower than what is traditionally accepted as a strong *n*.

While antagonist-based pharmacotherapies like naloxone and rimonabant are researched primarily for their main effects of treatment for addictive behaviors, often the side effects are listed as peripheral issues, instead of empirically isolating and testing them. This study represents a situation in which a specific side effect of the drugs was conceptualized, characterized, and tested on specific rat strains. Effects of these drugs on a nondrug reinforcer that may be suitable for establishing a drug-free lifestyle (i.e., exercise) were tested and dose-response information was established. For naloxone, it may be the case that compliance issues may relate to the drug in some manner by making other nondrug reinforcers less rewarding. Finding treatments to offset this, for example, using an opioid agonist such as buprenorphine (e.g., Orman & Keating, 2009a, 2009b) may restore this imbalance. For rimonabant, sensitivity to the higher doses of the drug may result in a heightened sensitivity to the general reward-suppressing effects of the drug, which may contribute to depression. It is important, though, that side effects for pharmacotherapies are more clearly defined, measured, and evaluated such that researchers and clinicians can better understand their effects on behavior. This study represents a first attempt at such an endeavor with rimonabant and naloxone.

References

- Agustín-Pavón, C., Martínez-Ricós, J., Martínez-García, F., & Lanuza, E. (1989). Sex versus sweet: Opposite effects of opioid drugs on the reward of sucrose and sexual pheromones. *Brain Research*, 492, 15–18.

- Banerji, M. A., & Tiewala, M. (2006). Rimonabant—the RIO North America trial: A new strategy to sustaining weight loss and related morbidity. *Current Diabetes Reports*, *6*, 228–229.
- Batki, S. L., Dimmock, J. A., Wade, M., Gately, P. W., Cornell, M., Maisto, S. A., . . . Ploutz-Snyder, R. (2007). Monitored naltrexone without counseling for alcohol abuse/dependence in schizophrenia-spectrum disorders. *The American Journal on Addictions*, *16*, 253–259.
- Beardsley, P. M., & Thomas, B. F. (2005). Current evidence supporting a role of cannabinoid CB1 receptor (CB1R) antagonists as potential pharmacotherapies for drug abuse disorders. *Behavioural Pharmacology*, *16*, 275–296.
- Beardsley, P. M., Thomas, B. F., & McMahon, L. R. (2009). Cannabinoid CB1 receptor antagonists as potential pharmacotherapies for drug abuse disorders. *International Review of Psychiatry*, *2*, 134–142.
- Belke, T. W. (1996). The effect of a change in body weight on running and responding reinforced by the opportunity to run. *The Psychological Record*, *36*, 421–433.
- Belke, T. W., & Christie-Fougere, M. M. (2006). Investigations of timing during the schedule and reinforcement intervals with wheel-running reinforcement. *Behavioural Processes*, *73*, 240–247.
- Belke, T. W., Pierce, W. D., & Jensen, K. (2004). Effect of short-term prefeeding and body weight on wheel running and responding reinforced by the opportunity to run in a wheel. *Behavioural Processes*, *67*, 1–10.
- Belke, T. W. (2004). Responding for sucrose and wheel-running reinforcement: Effect of body weight manipulation. *Behavioural Processes*, *65*, 189–199.
- Boer, D. P., Epling, W. F., Pierce, W. D., & Russell, J. C. (1990). Suppression of food deprivation-induced high-rate wheel running in rats. *Physiology and Behavior*, *48*, 339–342.
- Brown, R. A., Abrantes, A. M., Read, J. P., Marcus, B. H., Jakicic, J., Strong, D. R., . . . Gordon, A. (2009). Aerobic exercise for alcohol recovery: Rationale, program description, and preliminary findings. *Behavior Modification*, *33*, 220–249.
- Brown, R. A., Abrantes, A. M., Read, J. P., Marcus, B. H., Jakicic, J., Strong, D. R., . . . Gordon, A. (2010). A pilot study of aerobic exercise as an adjunctive treatment for drug dependence. *Mental Health and Physical Activity*, *3*, 27–34.
- Caille, S., & Parsons, L. H. (2006). Cannabinoid modulation of opiate reinforcement through the ventral striatopallidal pathway. *Neuropsychopharmacology*, *31*, 804–813.
- Carroll, M. E., Cosgrove, K. P., Campbell, U. C., Morgan, A. D., & Mickelberg, J. L. (2000). Reductions in ethanol, phencyclidine, and food-maintained behavior by naltrexone pretreatment in monkeys is enhanced by open economic conditions. *Psychopharmacology (Berlin)*, *148*, 412–422.
- Cohen, C., Kudas, E., & Griebel, G. (2005). CB1 receptor antagonists for the treatment of nicotine addiction. *Pharmacology, Biochemistry and Behavior*, *81*, 387–395.
- Cohen, C., Perrault, G., Griebel, G., & Soubrie, P. (2005). Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: Reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacology*, *30*, 145–155.
- Cohen, C., Perrault, G., Voltz, C., Steinberg, R., & Soubrie, P. (2002). SR141716, a central cannabinoid (CB1) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behavioural Pharmacology*, *13*, 451–463.
- Collier, G., & Hirsch, E. (1971). Reinforcing properties of spontaneous activity in the rat. *Journal of Comparative Physiology A. Sensory, Neural, and Behavioral Physiology*, *77*, 155–160.
- Connally, R. E. (1969). Instrumental conditioning of the running-wheel response of food-deprived rats. *Psychonomic Science*, *14*, 131–133.
- Cooper, Z. D., & Comer, S. D. (2009). Actions of drugs pertinent to their abuse: Targeting subjective, discriminative, and reinforcing effects for evaluation of potential substance-use therapies. In L. M. Cohen, F. Collins, A. Young, D. E. McChargue, T. R. Leffingwell & K. Cook (Eds.), *Pharmacology and treatment of substance abuse: Evidence- and outcome-based perspectives* (pp. 25–40). New York: Routledge/Taylor & Francis Group
- Costello, C. G. (1972). Depression: Loss of reinforcers or loss of reinforcer effectiveness? *Behavior Therapy*, *3*, 240–247.
- Daniel, M., Martin, A. D., & Carter, J. (1992). Opiate receptor blockade by naltrexone and mood state after acute physical activity. *British Journal of Sports Medicine*, *26*, 111–115.
- Davidson, D., Palfai, T., Bird, C., & Swift, R. (1999). Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcoholism, Clinical and Experimental Research*, *23*, 195–203.
- Despres, J. P., Golay, A., & Sjostrom, L. (2005). Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *New England Journal of Medicine*, *353*, 2121–2134.
- De Vries, T. J., & Schoffelmeer, A. N. (2005). Cannabinoid CB1 receptors control conditioned drug seeking. *Trends in Pharmacological Sciences*, *26*, 420–426.
- Dews, P. (1955). Studies on behavior. I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *Journal of Pharmacology and Experimental Therapeutics*, *113*, 393–401.
- Dubreucq, S., Koehl, M., Abrous, D. N., Marsicano, G., & Chaoloff, F. (2010). CB1 receptor deficiency decreases wheel-running activity: Consequences on emotional behaviours and hippocampal neurogenesis. *Experimental Neurology*, *224*, 106–113.
- Eikelboom, R., & Mills, R. (1988). A microanalysis of wheel running in male and female rats. *Physiology & Behavior*, *43*, 625–630.
- Escher, T., & Mittleman, G. (2006). Schedule-induced alcohol drinking: Non-selective effects of acamprosate and naltrexone. *Addiction Biology*, *11*, 55–63.
- European Medicines Agency. (2008). *Questions and answers on the recommendation to suspend the marketing authorisation of Acomplia (rimonabant)*. doi: Retrieved from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500014779.pdf
- Everson, E. S., Daley, A. J., & Ussher, M. (2008). The effects of moderate and vigorous exercise on desire to smoke, withdrawal symptoms and mood in abstaining young adult smokers. *Mental Health and Physical Activity*, *1*, 26–31.
- Forget, B., Barthelemy, S., Saurini, F., Hamon, M., & Thiebot, M. H. (2006). Differential involvement of the endocannabinoid system in short- and long-term expression of incentive learning supported by nicotine in rats. *Psychopharmacology (Berlin)*, *189*, 59–69.
- Forget, B., Hamon, M., & Thiebot, M. H. (2005). Cannabinoid CB1 receptors are involved in motivational effects of nicotine in rats. *Psychopharmacology (Berlin)*, *181*, 722–734.

- Galloway, G. P., Koch, M., Cello, R., & Smith, D. E. (2005). Pharmacokinetics, safety, and tolerability of a depot formulation of naltrexone in alcoholics: An open-label trial. *BMC Psychiatry*, *5*, 1–10.
- Glass, M. J., O'Hare, E., Cleary, J. P., Billington, C. J., & Levine, A. S. (1999). The effect of naloxone on food-motivated behavior in the obese Zucker rat. *Psychopharmacology*, *141*, 378–384.
- Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology (Berlin)*, *129*, 99–111.
- Higgins, S. T., Heil, S. H., & Lussier, J. P. (2004). Clinical implications of reinforcement as a determinant of substance use disorders. *Annual Review of Psychology*, *55*, 431–461.
- Hill, M. N., Titterness, A. K., Morrish, A. C., Carrier, E. J., Lee, T. T., Gil-Mohapel, J., . . . Christie, B. R. (2010). Endogenous cannabinoid signaling is required for voluntary exercise-induced enhancement of progenitor cell proliferation in the hippocampus. *Hippocampus*, *20*, 513–523.
- Iversen, I. H. (1993). Techniques for establishing schedules with wheel running as reinforcement in rats. *Journal of the Experimental Analysis of Behavior*, *60*, 219–218.
- Järvekülg, A., & Viru, A. (2002). Opioid receptor blockade eliminates mood effects of aerobic gymnastics. *International Journal of Sports Medicine*, *23*, 155–157.
- Kagan, J., & Brekun, M. (1953). The reward value of running activity. *Journal of Comparative Physiology A. Sensory, Neural, and Behavioral Physiology*, *47*, 108.
- Kamdar, N. K., Miller, S. A., Syed, Y. M., Bhayana, R., Gupta, T., & Rhodes, J. S. (2007). Acute effects of naltrexone and GBR 12909 on ethanol drinking-in-the-dark in C57BL/6J mice. *Psychopharmacology (Berlin)*, *192*, 207–217.
- Keeney, B. K., Raichlen, D. A., Meek, T. H., Wijeratne, R. S., Middleton, K. M., Gerdeman, G. L., & Garland, T. (2008). Differential response to a selective cannabinoid receptor antagonist (SR141716: Rimonabant) in female mice from lines selectively bred for high voluntary wheel-running behaviour. *Behavioural Pharmacology*, *19*, 812–820.
- Kirkham, T. C., & Williams, C. M. (2001). Synergistic effects of opioid and cannabinoid antagonists on food intake. *Psychopharmacology*, *153*, 267–270.
- Kodas, E., Cohen, C., Louis, C., & Griebel, G. (2007). Corticolimbic circuitry for conditioned nicotine-seeking behavior in rats involves endocannabinoid signaling. *Psychopharmacology (Berlin)*, *194*, 161–171.
- Le Foll, B., Forget, B., Aubin, H. J., & Goldberg, S. R. (2008). Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: Insights from pre-clinical and clinical studies. *Addiction Biology*, *13*, 239–252.
- Le Foll, B., & Goldberg, S. R. (2005). Cannabinoid CB1 receptor antagonists as promising new medications for drug dependence. *Journal of Pharmacology and Experimental Therapeutics*, *312*, 875–883.
- Mark, T. L., Kranzler, H. R., & Song, X. (2003). Understanding US addiction physicians' low rate of naltrexone prescription. *Drug and Alcohol Dependence*, *71*, 219–228.
- Markou, A., Weiss, F., Gold, L., Caine, B., Schulteis, G., & Koob, G. (1993). Animal models of drug craving. *Psychopharmacology*, *112*, 163–182.
- Navarro, M., Carrera, M. R., Del Arco, I., Trigo, J. M., Koob, G. F., & Rodriguez de Fonseca, F. (2004). Cannabinoid receptor antagonist reduces heroin self-administration only in dependent rats. *European Journal of Pharmacology*, *501*, 235–237.
- Orman, J. S., & Keating, G. M. (2009a). Buprenorphine/naloxone: A review of its use in the treatment of opioid dependence. *Drugs*, *69*, 577–607.
- Orman, J. S., & Keating, G. M. (2009b). Spotlight on buprenorphine/naloxone in the treatment of opioid dependence. *CNS Drugs*, *23*, 899–902.
- Pierce, W., Epling, D., Frank, W., & Boer, D. P. (1986). Deprivation and satiation: The interrelations between food and wheel running. *Journal of the Experimental Analysis of Behavior*, *46*, 199–210.
- Pillolla, G., Melis, M., Perra, S., Muntoni, A. L., Gessa, G. L., & Pistis, M. (2007). Medial forebrain bundle stimulation evokes endocannabinoid-mediated modulation of ventral tegmental area dopamine neuron firing in vivo. *Psychopharmacology (Berlin)*, *191*, 843–853.
- Pi-Sunyer, F. X., Aronne, L. J., Heshmati, H. M., Devin, J., & Rosenstock, J. (2006). Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: A randomized controlled trial. *Journal of the American Medical Association*, *295*, 761–775.
- Prochaska, J. J., Hall, S. M. H., Muñoz, R. F., Reus, V., & Hu, D. (2008). Physical activity as a strategy for maintaining tobacco abstinence: A randomized trial. *Preventive Medicine: An International Journal Devoted to Practice and Theory*, *47*, 215–220.
- Rasmussen, E. B., & Huskinson, S. L. (2008). Effects of rimonabant on behavior maintained by progressive ratio schedules of sucrose reinforcement in obese Zucker (*falfa*) rats. *Behavioural Pharmacology*, *19*, 735–742.
- Rasmussen, E. B., Reilly, W., & Hillman, C. (2010). Demand for sucrose reinforcement in lean and obese Zucker rats. *Behavioural Processes*, *85*, 191–197.
- Roberts, D., & Bennett, S. (1993). Heroin self-administration in rats under a progressive ratio schedule. *Psychopharmacology (Berlin)*, *111*, 215–218.
- Ross, S., & Peselow, E. (2009). Pharmacotherapy of addictive disorders. *Neuropharmacology*, *32*, 277–289.
- Samson, H. H., & Doyle, T. (1985). Oral ethanol self-administration in the rat: Effect of naloxone. *Pharmacology, Biochemistry, and Behavior*, *22*, 91–99.
- Scheen, A. J., Finer, N., Hollander, P., Jensen, M. D., & Van Gaal, L. F. (2006). Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: A randomised controlled study. *Lancet*, *368*, 1660–1672.
- Schneider, M., Heise, V., & Spanagel, R. (2000). Differential involvement of the opioid receptor antagonist naloxone in motivational and hedonic aspects of reward. *Behavioural Brain Research*, *117*, 163–171.
- Schull, J., Walker, J., Fitzgerald, K., & Hiilivirta, L. (1989). Effects of sex, thyro-parathyroidectomy, and light regime on levels and circadian rhythms of wheel-running in rats. *Physiology & Behavior*, *46*, 341–346.
- Schwartz-Stevens, K., Files, F., & Samson, H. H. (1992). Effects of morphine and naloxone on ethanol and sucrose-reinforced responding in nondeprived rats. *Alcoholism: Clinical and Experimental Research*, *16*, 822–832.
- Sharpe, A. L., & Samson, H. H. (2001). Effect of naloxone on appetitive and consummatory phases of ethanol self-administration. *Alcoholism: Clinical and Experimental Research*, *25*, 1006–1011.
- Sisti, H. M., & Lewis, M. J. (2001). Naloxone suppression and morphine enhancement of voluntary wheel-running activity in rats. *Pharmacology, Biochemistry, and Behavior*, *70*, 359–365.
- Smith, S., & Rasmussen, E. B. (2010). Effects of 2-AG on the reinforcing properties of wheel activity in obese and lean Zucker rats. *Behavioural Pharmacology*, *21*, 292–300.

- Solinas, M., & Goldberg, S. (2005). Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems. *Neuropsychopharmacology*, *30*, 2025–2035.
- Spanagel, R., Herz, A., Bals-Kubik, R., & Shippenberg, T. (1991). β -endorphin-induced locomotor stimulation and reinforcement are associated with an increase in dopamine release in the nucleus accumbens. *Psychopharmacology*, *104*, 51–56.
- Sparling, P. B., Giuffrida, A., Piomelli, D., Roskopf, L., & Dietrich, A. (2003). Exercise activates the endocannabinoid system. *Neuroreport*, *14*, 2209–2211.
- Stafford, D., LeSage, M. G., & Glowa, J. R. (1998). Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: A review. *Psychopharmacology*, *139*, 169–164.
- Stitzer, M., & Petry, N. (2006). Contingency management for treatment of substance abuse. *Annual Review of Clinical Psychology*, *2*, 411–434.
- Sullivan, M. A., Vosburg, S. K., & Comer, S. D. (2006). Depot naltrexone: Antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology (Berlin)*, *189*, 37–46.
- Tokuyama, K., Saito, M., & Okuda, H. (1982). Effects of wheel running on food intake and weight gain of male and female rats. *Physiology & Behavior*, *28*, 899–903.
- Trujillo, K., Belluzzi, J., & Stein, L. (1989a). Effects of opiate antagonists and their quaternary analogues on nucleus accumbens self-stimulation. *Behavioural Brain Research*, *33*, 181–188.
- Trujillo, K., Belluzzi, J., & Stein, L. (1989b). Opiate antagonists and self-stimulation: Extinction-like response patterns suggest selective reward deficit. *Behavioural Brain Research*, *492*, 15–28.
- United States Food and Drug Administration. (2007). Testimony before FDA Advisory Committee of rimonabant (HRG Publication #1815). Retrieved from: <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306oph1-01-Wolfe.pdf>
- Vlachou, S., Nomikos, G. G., & Panagis, G. (2006). Effects of endocannabinoid neurotransmission modulators on brain stimulation reward. *Psychopharmacology (Berlin)*, *188*, 293–305.
- Wakley, A. A., & Rasmussen, E. B. (2009). Effects of cannabinoid drugs on the reinforcing properties of food in gestationally undernourished rats. *Pharmacology, Biochemistry and Behavior*, *94*, 30–36.
- Walker, B. M., & Koob, G. F. (2008). Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. *Neuropsychopharmacology*, *33*, 643–652.
- Weinstock, J., Barry, D., & Petry, N. M. (2008). Exercise-related activities are associated with positive outcome in contingency management treatment for substance use disorders. *Addictive Behaviors*, *33*, 1072–1075.
- Williams, K. L., & Broadbridge, C. L. (2009). Potency of naltrexone to reduce ethanol self-administration in rats is greater for subcutaneous versus intraperitoneal injection. *Alcohol*, *43*, 119–126.
- Zurita, A., Martijena, I., Cuadra, G., Brandão, M., & Molina, V. (2010). Early exposure to chronic variable stress facilitates the occurrence of anhedonia and enhanced emotional reactions to novel stressors: Reversal by naltrexone pretreatment. *Behavioural Brain Research*, *208*, 466–472.

Received January 12, 2011

Revision received April 13, 2011

Accepted April 14, 2011 ■