Pharmacology, Biochemistry and Behavior 90 (2008) 701–711

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Rate-dependent effects of bupropion on nicotine self-administration and food-maintained responding in rats

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ARTICLE INFO

Article history:
Received 2 May 2007
Received in revised form 10 April 2008
Accepted 27 May 2008
Available online 3 June 2008

Keywords:
Bupropion
Nicotine self-administration
Non-specific effects
Rate-dependency
Rats

ABSTRACT

Bupropion has been found to be a useful pharmaceutical agent in furthering smoking abstinence. Preclinical research investigating the effects of bupropion on nicotine self-administration has indicated bupropion has selective effects on nicotine self-administration. However since response rates maintained by nicotine were significantly lower than rates of response maintained by the non-drug reinforcers, bupropion may have resulted in rate-dependent effects. The current experiments attempted to decrease the high response rate maintained through non-drug reinforcers in order to have more comparable control rates when investigating the selectivity of bupropion for nicotine self-administration. The effects of bupropion on nicotine self-administration (0.03 mg/kg/inf) were compared to food-maintained responding at two levels of food deprivation (deprived and satiated). Rats were satiated prior to the experimental session in order to decrease the overall response rates maintained through food reinforcement. Bupropion increased nicotine intake, but dose-dependently decreased food intake, when rats were food-deprived. However, when more comparable rates of behavior in the food-satiated group were investigated, bupropion had similar effects on nicotine and food-maintained responding. The data indicate that the effects of bupropion can be influenced by the control rate of responding. The results from these experiments also indicate that bupropion may not exert a selective effect on nicotine self-administration, since low rates of food and drug maintained responding were increased by the drug. These results indicate the importance of controlling for differences in response rates when attempting to assess the effects of drugs on responding maintained by different reinforcers. Furthermore, the results from the present study suggest that motivational variables (i.e. food deprivation) may be used to control for response rate differences maintained by drug and non-drug reinforcers.

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1. Introduction

The widespread compulsive use of tobacco products by the world's population has been associated with nearly 8.4 million tobacco-related deaths worldwide (Vainio et al., 2001). With 90% of the aversive health consequences being avoidable if individuals cease smoking by middle age (Peto et al., 2000), the benefits to the individual and society are immense. Traditional pharmaceutical treatments such as nicotine substitution therapy have improved rates of smoking cessation above levels found with placebo (Baska et al., 2004; Benowitz et al., 1998; Silagy et al., 2004; Transdermal Nicotine Study Group, 1991). Although nicotine replacement therapy increases rates of smoking abstinence, the use of the nicotine substitution therapy does not guarantee long term abstinence from smoking. In a review of the clinical trials, it was found that only 18% of individuals using nicotine replacement therapy combined with behavioral therapy maintained long term abstinence (Molyneux, 2004), thus pointing to a need for more effective pharmaceutical adjuncts in smoking cessation programs. Another current pharmacotherapy for nicotine addiction is the antidepressant bupropion. The clinical efficacy of bupropion in increasing rates of smoking abstinence was evaluated in two clinical studies which found bupropion performed better then placebo and the nicotine patch alone at increasing cessation rates (Hurt et al., 1997; Jorenby et al., 1999).

Recently the ability of bupropion to decrease the reinforcing properties of nicotine has been investigated using the drug self-administration procedure in rats (Bruijnzeel and Markou, 2003; Rauhut et al., 2003; Shoaib et al., 2003), which is commonly used as a preclinical screen for potential pharmacotherapies. In the drug self-administration procedure, rats are implanted with an indwelling jugular vein catheter which allows the animals to receive intravenous drug infusions. This model allows researchers to investigate the ability of novel compounds to alter nicotine self-administration. Typically when testing potential pharmacotherapeutics, researchers look for a compound that can decrease the number of drug infusions taken during an experimental session. It has been suggested that therapeutic

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doi:10.1016/j.pbb.2008.05.014

compounds for drug abuse should exert a selective effect on drug intake; thus diminishing the likelihood that non-drug related factors were involved in the observed effect (Mello, 1992). Usually this is accomplished by testing the compound on behavior maintained by other events, such as food or sucrose.

Recent studies have investigated the ability of bupropion to selectively decrease nicotine self-administration by comparing the drug's effect on sucrose and food-maintained behavior (Bruijnzeel and Markou, 2003; Rauhut et al., 2003). Although researchers have investigated the selectivity of bupropion using the rodent nicotine self-administration model, few researchers have considered the potential involvement of rate-dependency; the notion that different control rates of responding can alter a drug's effect on behavior. It is widely known in behavioral pharmacology that stimulants tend to increase low rates of behavior and decrease high rates of schedule-controlled behavior (Dews, 1958; McMillan and Leander, 1976).

In one study, Rauhut et al. (2003) found that bupropion increased nicotine self-administration in a biphasic manner, with low to medium doses (9–26 mg/kg) increasing responding, and larger doses (52–78 mg/kg) decreasing nicotine self-administration. In that study, bupropion dose-dependently decreased sucrose-maintained responding, indicating a selective effect on nicotine self-administration. Bruijnzeel and Markou (2003) found a greater decrease in nicotine self-administration compared to food-maintained responding under a fixed-ratio (FR) schedule of reinforcement. Moreover, bupropion increased only food-maintained responding when either nicotine or food was delivered under a progressive-ratio schedule (PR). Both the Rauhut et al. (2003) and the Bruijnzeel and Markou (2003) studies found that bupropion had selective effects on nicotine self-administration, although the studies had different results on nicotine self-administration. A potential reason for the discrepancies is that bupropion could be having non-specific effects on low rates of responding regardless of the event maintaining behavior. Since nicotine typically maintains response rates considerably lower than responding maintained by other reinforcers (Risner and Goldberg, 1983; Rose and Corrigall, 1997), rate-dependency could potentially be confounding the interpretation of drug selectivity.

Neither of the two previous experiments which found selective effects of bupropion on nicotine self-administration attempted to control for the different rates of responding maintained by the drug and non-drug reinforcers (Bruijnzeel and Markou, 2003; Rauhut et al., 2003). The major goal of the present study was to determine the extent to which bupropion has non-specific effects on nicotine self-administration. To accomplish this goal, the effects of bupropion were evaluated on moderate or low rates of food-maintained responding, and on low rates of nicotine-maintained responding. The response rates maintained through food reinforcement were manipulated in the present study by feeding rats before the experimental session, thus decreasing the motivation or saliency of the food pellet during subsequent operant sessions.

2. Materials and methods

2.1. Animals

Male Sprague Dawley rats were used for the nicotine (n=7) and food-satiated (n=4) experiments and male Fisher 344 rats were used in the food-deprived (n=4) experiment. All rats were obtained from Harlan Inc. Rats were approximately two months old at the start of the experiments and maintained weights of approximately 300 g through out the experiment. Upon arrival to the colony, rats were individually housed in hanging metal cages and allowed to acclimate to the laboratory for seven days during which time they had *ad libitum* access to food and water. Rats used in the nicotine self-administration condition were individually housed in Plexiglas cages following surgery, under a reverse light–dark cycle (lights on from 19:00 to 07:00) and given unlimited access to water except during experimental sessions. Rats in both food conditions were individually housed in hanging metal cages during the duration of the experiments and were also under a reverse light–dark cycle (lights on from 19:00 to 07:00) and given unlimited access to water except during experimental sessions.

2.2. Apparatus

Six custom built operant chambers, located inside a sound-attenuating box, consisted of two Plexiglas side walls with the front and back wall constructed of aluminum. On the front wall of the chamber was an active lever, requiring approximately 0.25 N to register a response. A green-jeweled stimulus light was centered above the active lever and a food cup was located to the left of the active lever. An inactive lever (had no programmed consequences) was centered below a red-jeweled stimulus light on the back wall. Located outside the operant chambers were a food pellet dispenser, tone generator, ventilation fan, high speed infusion pump (Med Associates, PHM-103), and a white houselight.

2.3. Nicotine self-administration

The nicotine self-administration procedure used in the current experiment was similar to that reported by Corrigall and Coen (1989). The rats were given 10 g of the food pellets in their home cages 48 h prior to the start of training (45 mg pellets; BioServ, Frenchtown, NJ). Responses on the active lever initially resulted in the delivery of a food pellet under a fixed-ratio (FR) 1 60-s timeout (TO) schedule of reinforcement. Each press on the active lever also resulted in a brief flash of the stimulus lights above both the active and inactive levers. The delivery of each reinforcer resulted in the activation of a tone which remained on during the 60-s TO. The subjects remained on an FR1 60-s TO schedule of reinforcement until the animals earned a minimum of 20 reinforcers in a 60-min session and the number of active lever presses were more than the number of inactive lever presses. The lever press response was typically acquired with 2–3 experimental sessions.

Following acquisition of the lever press response, rats were given ad libitum access to standard rat chow in order to regain their free-feeding body weights. Following recover of free-feeding body weights, rats underwent catheterization surgery. Following a seven day recovery from surgery rats acquired i.v. nicotine self-administration (0.03 mg/kg/infusion) under an FR1 60-s TO schedule of reinforcement during daily 60-min experimental sessions. The same discriminative stimuli were used during nicotine self-administration as those previously described during initial lever press training. Responses on the active lever resulted in the delivery of nicotine infusions, while responses on the inactive lever were recorded but had no scheduled consequence. Responses on the active lever during TO periods were also recorded but had no scheduled consequence. Nicotine self-administration was maintained on an FR1 for five consecutive sessions. Following the five consecutive session, the required ratio was increased to an FR2 for three sessions and finally to a terminal FR3 schedule of reinforcement. Before the administration of bupropion, the following criteria for stable responding on the terminal schedule were required: five or more infusions per session for five consecutive sessions without the number of infusions during the session increasing or decreasing by more than seven infusions. Rats typically met the stability criterion within 15–20 experimental sessions. Following the experimental sessions, the rats were fed 15 g of standard rat chow. Previous research in our laboratory has indicated the current level of food deprivation is required in order to maintain significant levels of nicotine intake.

2.4. Catheterization surgery

Rats were anesthetized with intraperitoneal (i.p.) injections of sodium pentobarbital (Nembutal, 40 mg/kg) and atropine sulfate

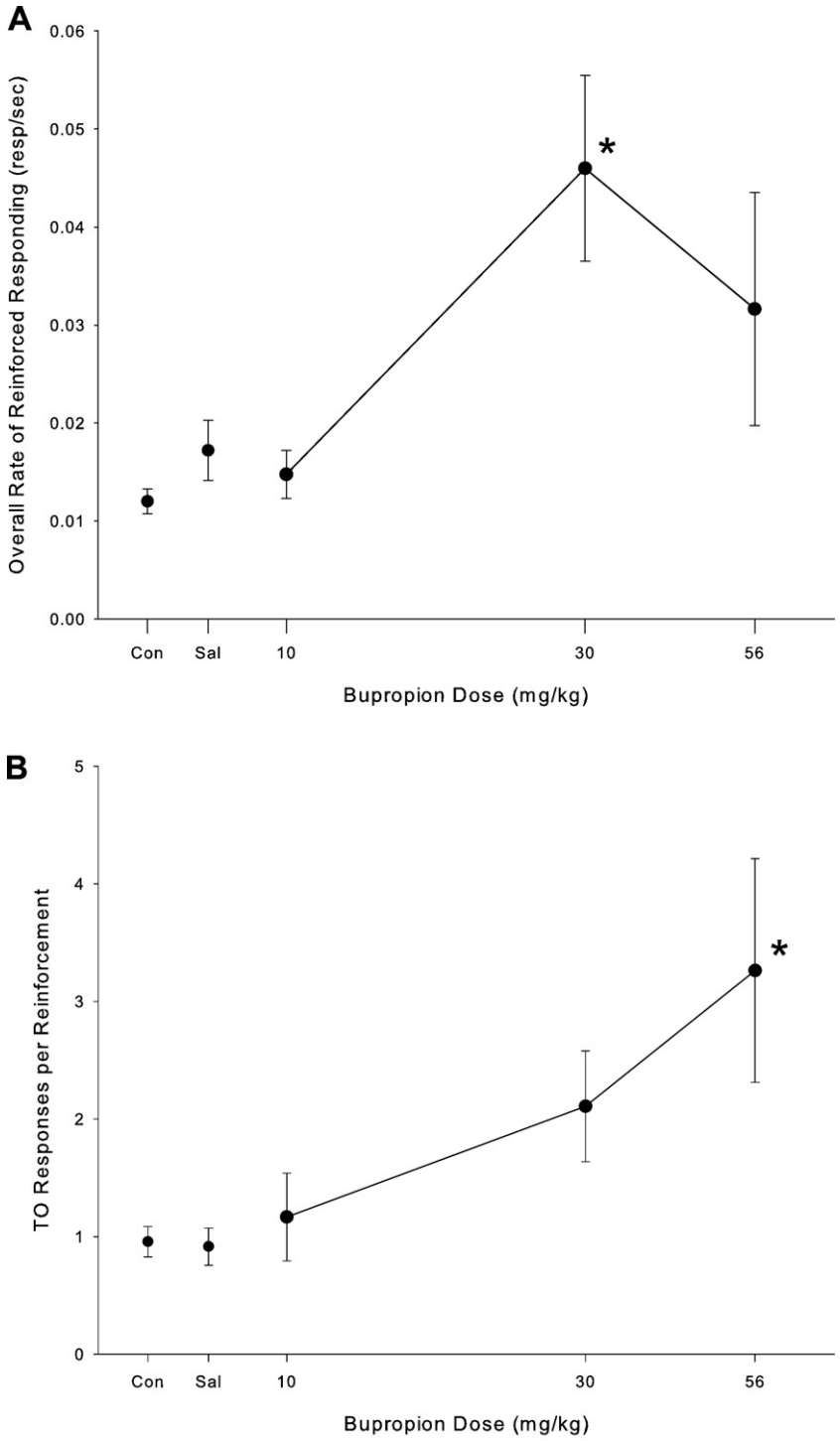

Fig. 1. The effects of bupropion pretreatments (0, 10, 30 and 56 mg/kg) on nicotine self-administration. Data are expressed as the mean overall response rates (±SEM). A) Effects of bupropion on the overall response rate (responses/s) on the active lever. B) Effects of bupropion on the number of timeout responses on the active responses per reinforcer earned. * indicates a significant difference from saline injections ($N=7$).

(10 mg/kg). A polyvinyl catheter was inserted into the right facial vein, and subcutaneously exited out the back of the animal through a polycarbonate back-plate implanted under the skin. The catheter was then passed through a spring leash and connected to a liquid swivel. The liquid swivel was connected to a counter balance arm which allowed the animal relatively unrestricted movement. In order to maintain catheter patency, the catheters were automatically flushed every 90 min with heparinized saline (1.7 U/ml). The flushing of the catheters was done via a pump which was connected to the liquid swivels while the animals were in their home cage. The rats were given a seven day recovery period following surgery before self-administration sessions began.

2.5. Food-maintained responding in food-deprived rats

The procedure for this experiment was similar to that used for the nicotine self-administration experiment; except that rats did not undergo surgery and food pellets maintained responding for the

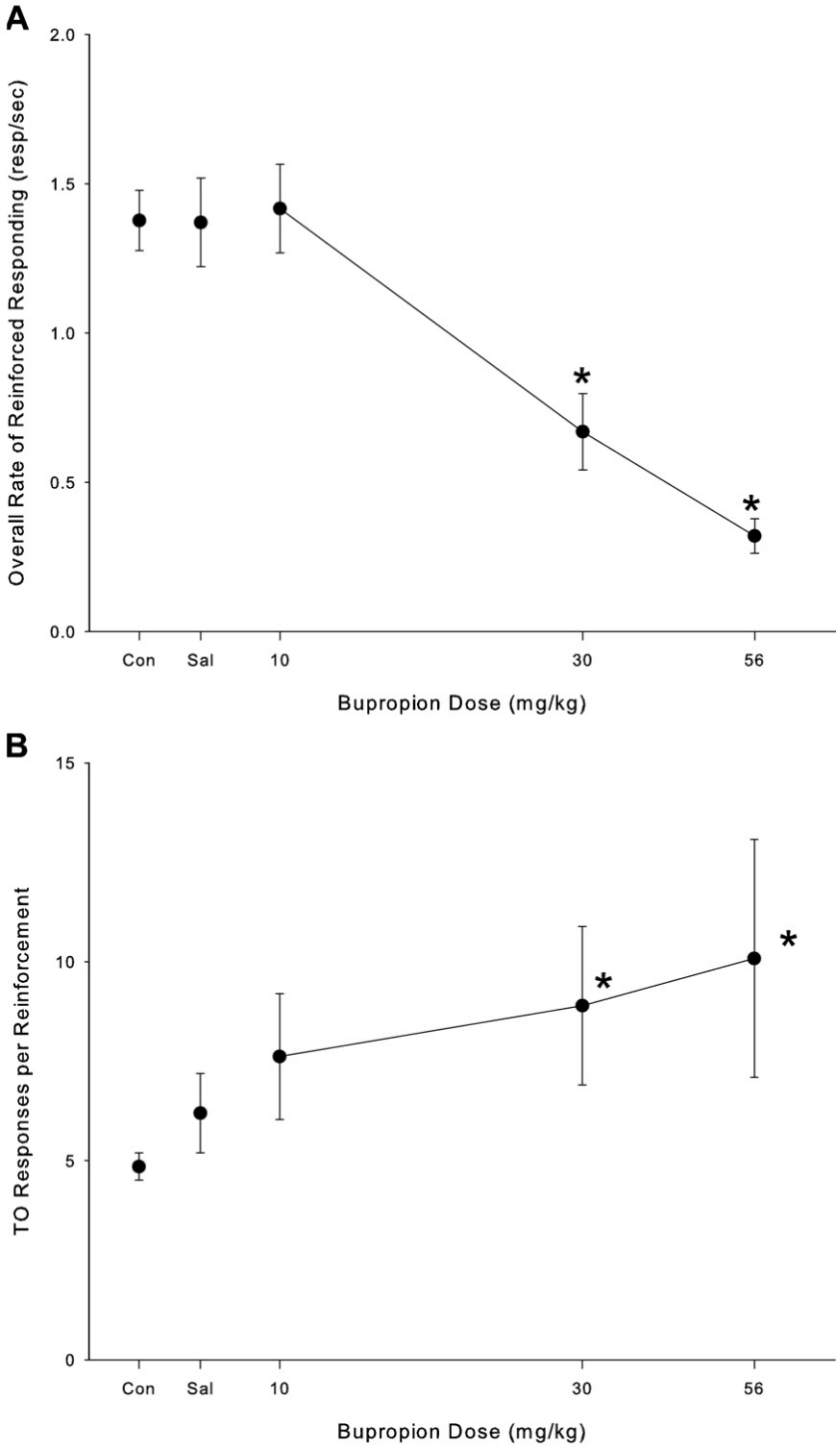

Fig. 2. The effects of bupropion pretreatments (0, 10, 30 and 56 mg/kg) on behavior maintained through food reinforcement in food-deprived rats. Data are expressed as the mean overall response rates (±SEM). A) Effects of bupropion on the overall response rate (responses/s) on the active lever. B) Effects of bupropion on the number of timeout responses on the active lever per reinforcer earned. * indicates a significant difference from saline injections (N=4).

duration of the experiment. Also, the acquisition to a terminal schedule of FR5 60-s TO was different than the nicotine self-administration experiment, in that, the ratio value increased from an FR1 to an FR3 and finally to an FR5 over five sessions. The same food pellets and discriminative stimuli as described in the nicotine self-administration experiment were used in this experiment. Before the administration of bupropion the following stability criterion were required: the number of reinforcers obtained within a session did not fluctuate by more than two reinforcers for five consecutive sessions. Thirty minutes following experimental sessions, rats were fed 20 g of rat chow.

2.6. Food-maintained responding in food-satiated rats

In order to decrease the high rates of response maintained by food-deprived rats in the previously described experiment, rats were fed 25 g of rat chow 90 min prior to the start of experimental sessions. All

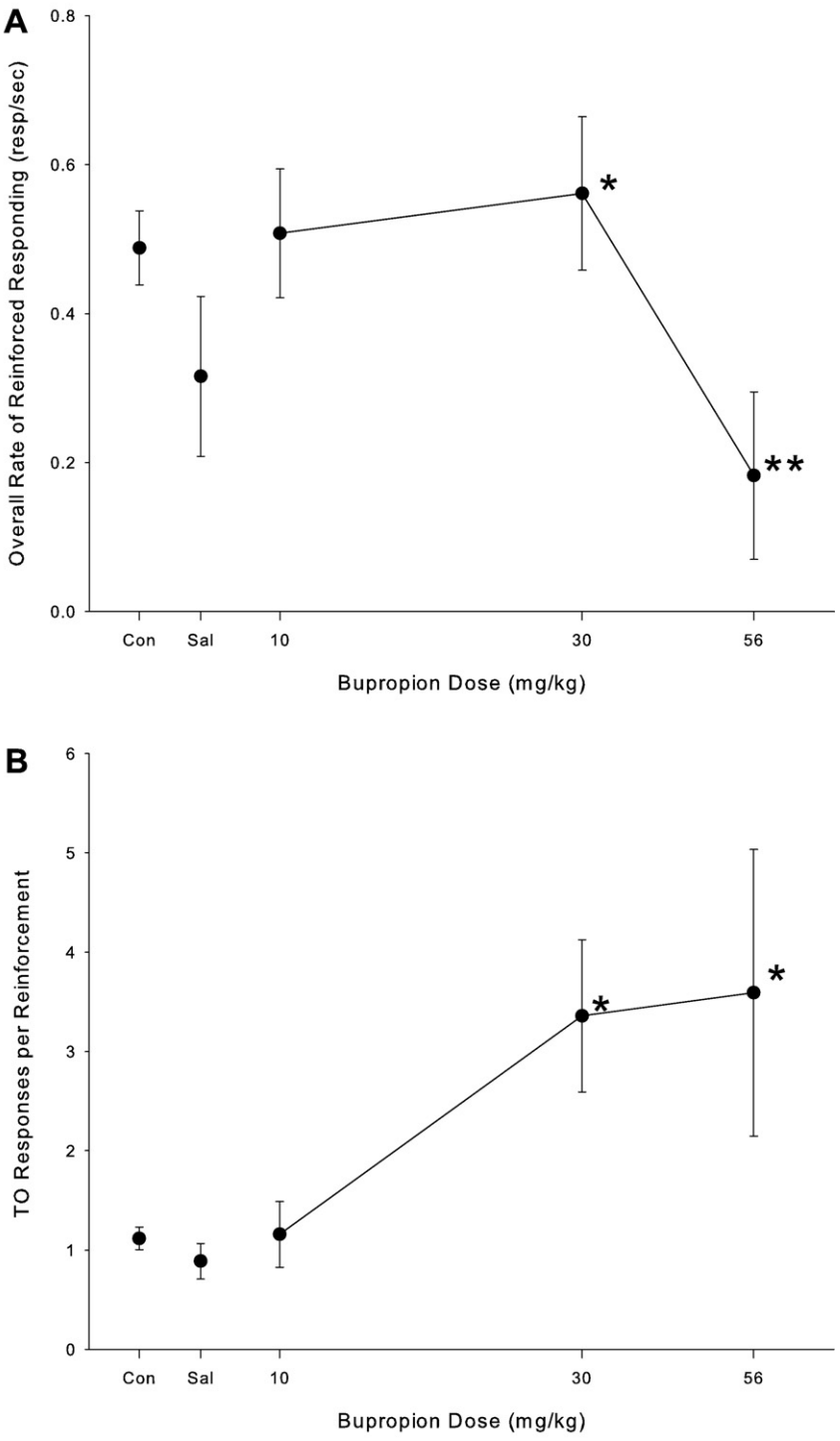

Fig. 3. The effects of bupropion pretreatments (0, 10, 30 and 56 mg/kg) on behavior maintained through food reinforcement in food-satiated rats. Data are expressed as the mean overall response rates (±SEM). A) Effects of bupropion on the overall response rate (responses/s) on the active lever. B) Effects of bupropion on the number of timeout responses on the active lever per reinforcer earned. * indicates a significant difference from saline injections, ** indicates a significant difference compared to control levels (days prior to injections; $N=4$).

other procedural details were as described in the food-deprived condition. Before the administration of bupropion the following stability criterion was required: the number of reinforcers did not fluctuate by more than seven reinforcers over five consecutive sessions. The addition of this criterion in the food-satiation procedure was necessitated by the increased variability in the number of reinforcers obtained within an experimental session.

2.7. Bupropion pretreatments

Once responding was stable, rats were administered 15-min pretreatments of varying doses of bupropion (0, 10, 30 and 56 mg/kg; i.p.) prior to the start of an experimental session. Each dose of bupropion was administered at least twice in a pseudorandom order. Following each pretreatment session rats were given at least two

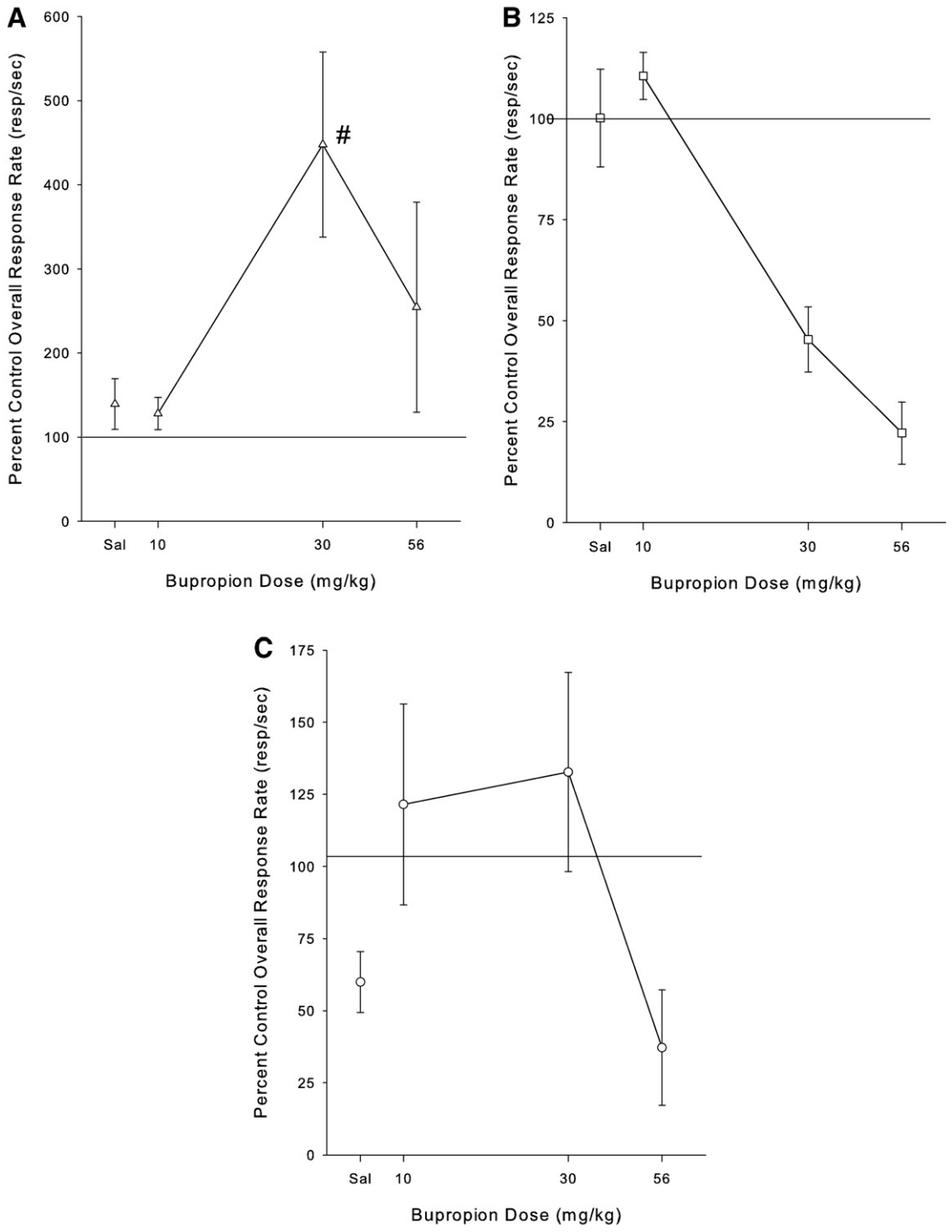

Fig. 4. The percent change in the overall response rates for the three experimental conditions following bupropion pretreatments (0, 10, 30 and 56 mg/kg). A) percent change in overall response rates maintained through nicotine infusions, B) percent change in overall response rates maintained through food reinforcement in food-deprived rats, C) percent change in overall response rates maintained through food reinforcement in food-satiated rats. # indicates significantly different than responding under food-deprived condition at equivalent dose ($p<.05$).

sessions in which no pretreatment was given in order for responding to return to baseline levels.

2.8. Drugs

S(−)-Nicotine bitartrate was purchased from RBI (Natick, MA). The nicotine solution for i.v. nicotine self-administration was dissolved in heparinized 0.9% physiological saline and was adjusted to a pH of 7 using sodium hydroxide. Nicotine was delivered at a dose of 0.03 mg/kg (free base) of the animal's body weight at a volume of 50 μl at 10 μl/0.1 s Bupropion (2-(*tert*-butylamino)-3'-chloropropio-phenone fumarate) was supplied by the Research Triangle Institute (Research Triangle Park, NC) and dissolved in 0.9% physiological saline, and injected in a volume of 2.0 ml/mg of the drug. Catheter patency was checked every two weeks using sodium methohexital (Brevital, 0.2 mg/injection). Patency was indicated by a loss of consciousness within five s.

2.9. Data analysis

Data from all experiments were analyzed using a repeated measures analysis of variance (ANOVA). Post hoc comparisons of interest were conducted using paired *t*-tests for all between and within-group comparisons. Results were deemed significant at $p<0.05$. The main dependent variables of interest for the three experiments were overall response rate (responses/s; not including responses made during timeout), inactive lever response rate (responses/s), and the number of timeout responses per reinforcer (total number of TO responses/total number of reinforcers obtained within the session).

Rate-dependent effects of bupropion were investigated by analyzing the correlation between the change in the overall response rates following bupropion pretreatments and the overall response rates on control days (days prior to a bupropion pretreatments). The percent change in overall response rate from control levels for each drug dose were plotted against the control overall response rate on a log, log scale (referred to as rate-dependency plots). Trend lines were fit to the data points on each graph and the r^2 values for the trend line are displayed on the graphs. One way

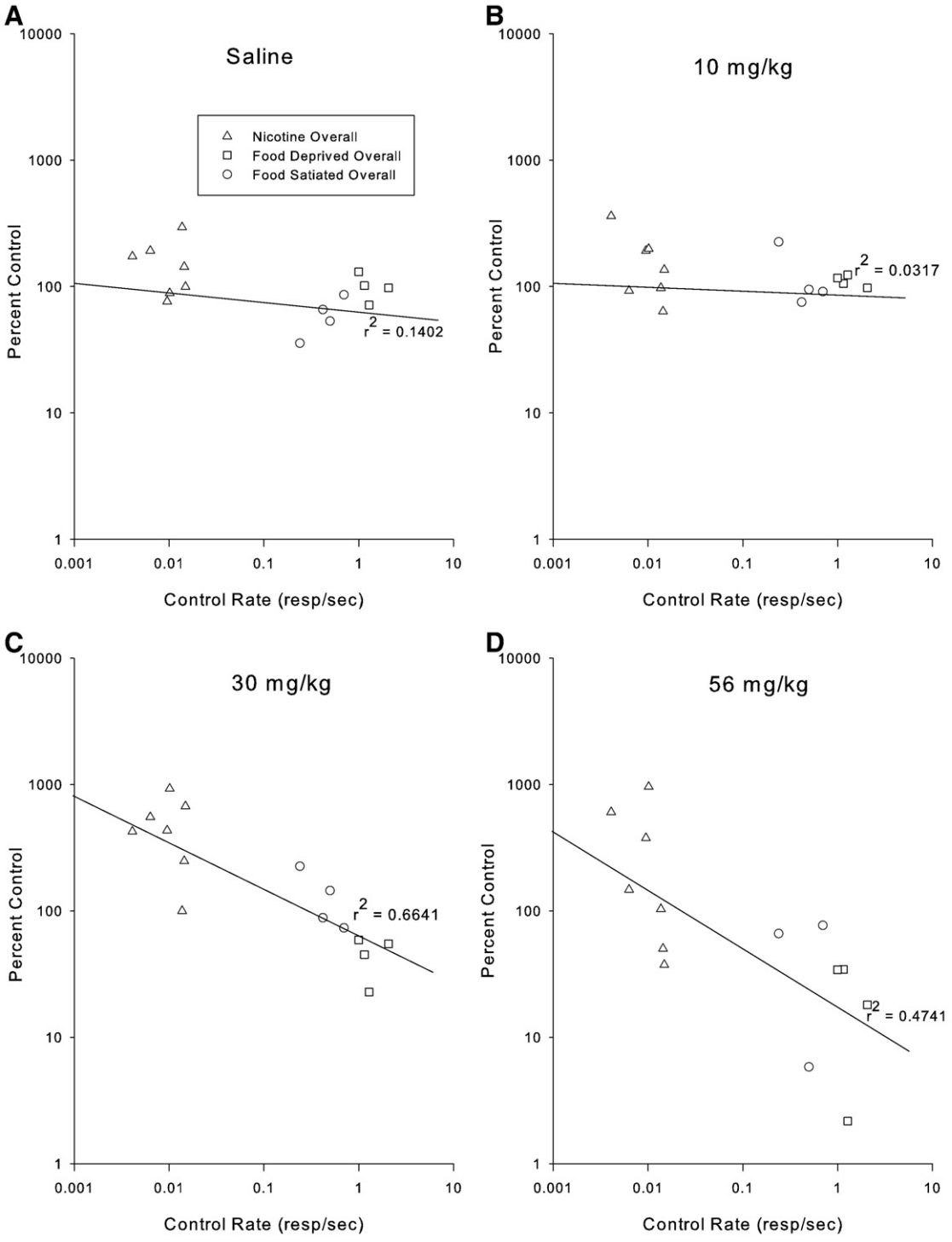

Fig. 5. Rate-dependency plots of the overall response rates from the three experiments. A) percent change in overall response rates following the administration of saline, B) 10 mg/kg dose of bupropion, C) 30 mg/kg dose of bupropion, D) and 56 mg/kg dose of bupropion.

ANOVAs were conducted to test for significant correlation coefficients (r^2) for the regressions conducted on the rate-dependency plots.

3. Results

3.1. Dose effect of bupropion on nicotine self-administration

The group averages for the overall response rate are shown in Fig. 1A. A repeated measures ANOVA revealed a main effect of dose [$F(4, 77)=3.773$, $p<.01$]. Post hoc comparisons revealed the 30 mg/kg dose of bupropion significantly increased the overall response rates above levels seen following saline injections. A repeated measures ANOVA on the number of timeout responses per reinforcement [$F(4, 77)=6.216$, $p<.001$; Fig. 1B] and inactive lever responding [$F(4, 77)=5.729$, $p<.001$; data not shown] resulted in main effect of dose. Post hoc comparisons revealed that the highest dose of bupropion (56 mg/kg) significantly increased both the number of timeout responses and the number of inactive lever responses above levels seen following saline injections.

3.2. Dose effect of bupropion on food-maintained responding in food-deprived rats

The administration of bupropion resulted in a dose-dependent decrease in the overall response rates on high rates of behavior

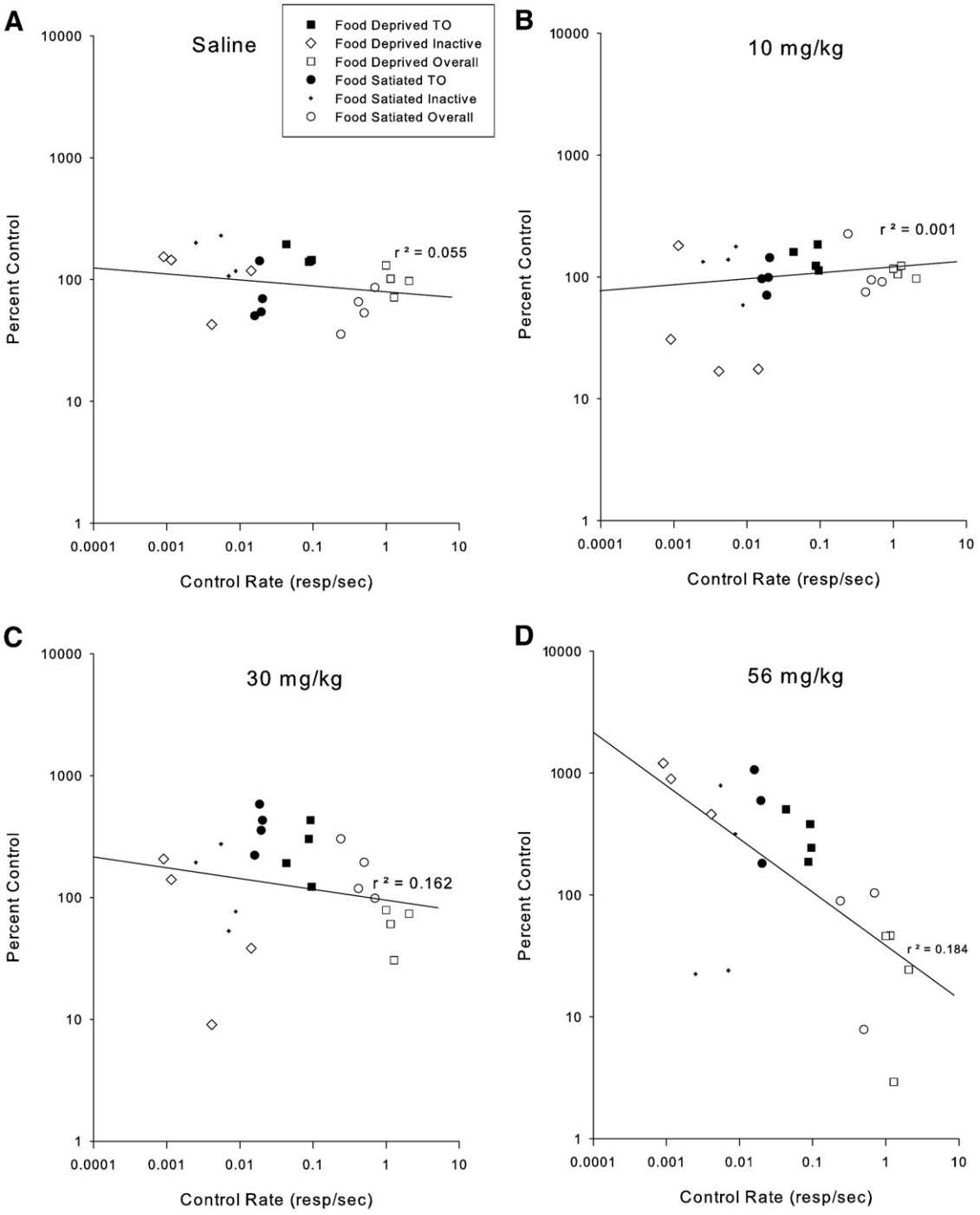

Fig. 6. Rate-dependency plots of the overall, inactive, and timeout response rates when behavior was maintained by a non-drug reinforcer (i.e. food pellets). A) percent change in response rates following the administration of saline, B) 10 mg/kg dose of bupropion, C) 30 mg/kg dose of bupropion, D) and 56 mg/kg dose of bupropion.

maintained by food reinforcement (Fig. 2A). A repeated measures ANOVA revealed a main effect of dose [$F(4, 56) = 11.923$, $p < .001$]. Post hoc comparisons revealed the two highest doses of bupropion significantly decreased responding compared to levels seen following saline injections. A repeated measures ANOVA revealed a significant dose-dependent increase in the number of timeout responses [$F(4, 56) = 3.000$, $p = .026$; Fig. 2B]. Post hoc comparisons indicated that the two highest doses of bupropion (30 and 56 mg/kg) resulted in significant increases in the number of timeout responses compared to levels seen following saline injections. There were no significant effects of bupropion on the number of inactive lever responses in food-deprived rats.

3.3. Dose effect of bupropion on food-maintained responding in food-satiated rats

In order to determine the ability of food-satiation to decrease overall response rates a one-way ANOVA was conducted on the overall response rates maintained across the three conditions. The ANOVA revealed a significant effect between the overall response rates in the three experiments [$F(2, 12) = 36.46$, $p < .001$]. Post hoc comparisons revealed that food-satiation significantly decreased the overall response rates compared to response rates obtained in the food-deprived experiment ($p < .001$). Post hoc comparisons also revealed that overall response rates maintained through food-satiation were also significantly higher then those maintained through nicotine reinforcement ($p = .044$). The overall response rates for the food-satiated rats are shown in Fig. 3A. A repeated measures ANOVA indicated a main effect of dose [$F(4, 53) = 2.799$, $p < .05$]. Post hoc comparisons revealed that only the highest dose of bupropion (56 mg/kg) significantly decreased food-maintained responding when rats were food-satiated. A repeated measures ANOVA also revealed a significant effect of dose on the number of timeout responses [$F(4, 51) = 5.122$, $p < .01$; Fig. 3B]. Post hoc comparisons indicated that two highest doses of bupropion (30 and 56 mg/kg) resulted in significant increases in the number of timeout responses compared to levels seen following saline injections. There were no significant effects of bupropion on the number of inactive lever responses in food-satiated rats.

3.4. Comparing the effects of bupropion across experiments

3.4.1. Dose effect of bupropion across experiments

In order to determine whether bupropion had differential effects on the overall response rates across the different experimental conditions (nicotine self-administration, food-deprived and food-satiated), the overall response rates were represented as a percent change from control levels. The dose response curves are illustrated in Fig. 4. The percent change in the overall response rate following bupropion pretreatments were analyzed using a mixed factor ANOVA with dose as a within-subject factor and experimental condition as a between-subject factor. The mixed factor ANOVA revealed there was no significant effect of dose [$F(3, 36) = 1.781$, $p = .168$], but did reveal a significant interaction between dose and experimental condition [$F(6, 36) = 2.442$, $p < .05$]. Post hoc analysis revealed that following pretreatment with the 30 mg/kg dose of bupropion responding maintained by nicotine infusions and food pellets increased, but food-maintained responding only increased under food-satiated conditions. While the 30 mg/kg dose of bupropion increased food-maintained responding under food-satiated conditions, the same dose of bupropion decreased food-maintained responding under food-deprived conditions. These results indicate that bupropion may not be having drug selective effects when the overall response rates maintained by food were lowered to a more comparable level.

3.4.2. Rate-dependent effects of bupropion

To evaluate potential rate-dependent effects of bupropion, the percent change from control for the overall response rates under the different conditions were plotted using rate-dependency plots. The rate-dependency plots for each dose of bupropion are shown in Fig. 5. The one-way ANOVA on the overall response rates following the 30 mg/kg dose of bupropion resulted in a significant correlation between the percentage of change following bupropion pretreatment and the control rate of response [$r^2 = 0.6641$; $F(1, 13) = 8.589$, $p = 0.012$] indicating a significant rate-dependent effect (Fig. 5C). Pretreatment with the 56 mg/kg dose of bupropion resulted in a trend toward a rate-dependent effect, although the correlation coefficient ($r^2 = 0.4741$) failed to reach statistical significance (Fig. 5D).

In order to strengthen the argument that bupropion was having rate-dependent effects, all behaviors maintained by the non-drug reinforcer (i.e. food pellets) were plotted using rate-dependency plots. The rate-dependency plots for each dose of bupropion are shown in Fig. 6. A one-way ANOVA on the overall, inactive and timeout response rates following the 30 mg/kg dose of bupropion resulted in a significant correlation between the percentage of change following bupropion pretreatment and the control rate of response [$r^2 = 0.162$; $F(1, 23) = 4.26$, $p = 0.05$] indicating a significant rate-dependent effect (Fig. 6C). Also, a one-way ANOVA on the overall, inactive and timeout response rates following the 56 mg/kg dose of bupropion resulted in a significant correlation [$r^2 = 0.184$; $F(1, 23) = 4.95$, $p = 0.03$; Fig. 6D].

4. Discussion

The effects of bupropion on nicotine self-administration in the current experiment are similar to those previously reported (Rauhut et al., 2003). In the current study, moderate doses of bupropion resulted in significant increases in nicotine self-administration while low and high doses did not, this is similar to that seen in the Rauhut et al. (2003) study, at two different doses of nicotine (0.01 and 0.02 mg/kg/infusion). The increasing effect of bupropion on nicotine intake is also congruent with a study which found that acute doses of oral bupropion resulted in increases in the number of cigarettes smoked in humans (Cousins et al., 2001). The current experiment found that bupropion dose-dependently decreased food-maintained responding when the animals were food-deprived. Again, these results are also congruent with results from the Rauhut et al. (2003) study, which found dose-dependent decreases in sucrose-maintained responding. Results from the food-satiated condition indicate that bupropion at a moderate dose (30 mg/kg) can increase behavior maintained through food reinforcement when the overall response rates are decreased by food-satiation.

Bupropion resulted in dose-dependent increases in the number of timeout responses, in both the nicotine self-administration study and the food studies. High doses of bupropion also increased inactive lever responding in the nicotine self-administration experiment. The increases in both timeout and inactive lever responding in nicotine self-administration have not been reported in previous studies (Bruijnzeel and Markou, 2003; Rauhut et al., 2003; Shoaib et al., 2003). The increasing effects of bupropion on timeout responding are the first to indicate that bupropion can increase behavior suppressed by punishment. Previous research has shown that there are differential drug effects depending on whether operant behavior is suppressed through negative punishment or positive punishment (Branch et al., 1977). Psychostimulants such as amphetamine and cocaine have been shown to decrease operant responding which is suppressed through positive punishment (Glowa, 1986), while amphetamine has been found to increase schedule-induced drinking reduced through negative punishment (Perez-Padilla and Pellon, 2003). The current findings add to this literature, in that, the psychostimulant bupropion increases operant responding which is suppressed through negative punishment (i.e. TO) regardless of whether the reinforcer is a drug or non-drug.

There are several mechanism by which bupropion could be increasing the number of timeout responses. One potential mechanism is that

bupropion could be resulting in a loss of stimulus control leading to increased responding during the timeout period. Previous literature has shown that stimulant drugs such as amphetamine result in a loss of discriminative control (Katz, 1988). A second potential mechanism for the increase in timeout response is that bupropion may be increasing the value of a delayed reinforcer, which has been shown previous with the stimulant, amphetamine (LeSage et al., 1996; Richards et al., 1999). It is possible that bupropion may be increasing the value of the reinforcer following the timeout by increasing the animals "internal clock" resulting in a subjective shorting of the timeout period. This would be congruent with previous literature indicating that methamphetamine increases the internal clock of animals on a discrimination task (Maricq et al., 1981). Another potential explanation for the increase in the number timeout responses following bupropion pretreatment is that bupropion may be having rate-dependent effects, that is, bupropion is increasing the low rate of responding maintained during timeout periods.

Previous studies evaluating the effects of bupropion on nicotine self-administration have indicated that bupropion has selective effects on nicotine self-administration (Bruijnzeel and Markou, 2003; Rauhut et al., 2003). While the data from the previous studies does support this conclusion, neither study attempted to control for the higher rates of responding engendered by food or sucrose reinforcers. Given that the administration of stimulants are known to have rate-dependent effects on schedule-controlled behavior (Sanger and Blackman, 1976), it is interesting that most drug selectivity experiments often overlook differences in rates of responding between drug and non-drug reinforcers. The current study found that when the rates of responding between drug and non-drug reinforcers are considered, bupropion had a similar effect on food and nicotine self-administration.

The current data suggests that the effect of bupropion on nicotine self-administration may not be a result of the drug altering the reinforcing properties of nicotine. A rate-dependency description of the data may be more applicable; that is, the effect of bupropion on nicotine self-administration is influenced by the ongoing low rate of behavior. The rate-dependent effects on the overall response rates maintained by the nicotine and food studies indicate the effects of bupropion were dependent on the control rates of responding. Also, when only behaviors maintained under the food-schedules were analyzed for rate-dependent effects the higher doses of bupropion were again increasing low rates of responding (i.e. timeout and inactive lever responding) while decreasing higher rates of behavior. Effects of bupropion on schedule-controlled behavior have been reported previously. Bupropion has been reported to increased low rates of response in an fixed-interval (FI) component, while not affecting high rates of behavior in an FR component of a multiple FI FR schedule (McKearney, 1982). Bupropion has also been shown to increase low rates of response under a simple FI schedule of reinforcement in monkeys (Spealman et al., 1989).

The current experiment indicates that the increasing effect of bupropion on behavior can be independent of the events (nicotine or food) maintaining behavior. Previous research has shown that rate-dependent effects of stimulants on schedule-controlled behavior are independent of the maintaining event (Kelleher and Morse, 1968). For instance, Branch (1979) found that cocaine and D-amphetamine resulted in rate-dependent effects regardless whether the behavior was maintained through negative reinforcement, food presentation, or the presentation of electric shock. A second study found that monoamine reuptake inhibitors resulted in similar effects on both cocaine self-administration and food-maintained behavior under a multiple schedule of reinforcement (Kleven and Woolverton, 1993).

While the current data indicate that bupropion may be having rate-dependent effects, a caveat in the current studies is that different rat strains (Sprague Dawley vs. Fisher 344) were used to assess the effect of bupropion on overall response rates under food-deprived and food-satiated conditions. In the current study the high rate of behavior which was decreased by bupropion was maintained in Fisher 344 rats, where as a moderate rates of behavior maintained in food-satiated Sprague Dawley rats were increased with the 30 mg/kg dose of bupropion, qualitatively similar to the increases seen in nicotine self-administration, also in Sprague Dawley rats. It could be argued that increases following the 30 mg/kg dose of bupropion are a result of the strain of the animal not the rate of responding. Although, previous literature indicates it is the rate of responding that is the determining factor in the effect of bupropion (Rauhut et al., 2003). In Rauhut et al. (2003), the high rate of behavior was maintained in Sprague Dawley rats and bupropion was found to decrease responding. While the differences in strains in the could be a potential confound, it seems more likely the effects of bupropion are due to rate-dependency rather than an effect of rat strain given the effects of bupropion in the Rauhut et al. (2003) study.

Although satiating the animals prior to the experimental session did not result in the in the response rates being identical to rates maintained by nicotine infusions, there are a limited number of manipulations that will decrease responding while keeping the reinforcement schedules similar. Only one previous nicotine self-administration study has attempted to equate nicotine and food response rates, while keeping similar schedules of reinforcement. Paterson et al. (2003) attempted to equate responding by placing long timeout components in the schedule maintained by food delivery (Paterson et al., 2003). This timeout manipulation most likely only alters reinforcer density (i.e. number of reinforcers earned in a session) and does not decrease the rate of response once reinforcement is available. Food satiating the animals prior to an experimental session is a manipulation which can produce a substantial decrease in response rates without systematically changing reinforcement frequency or density.

The apparent rate-dependent effects of bupropion found in the current experiment could lend insight into a potential mechanism for how bupropion affects smoking cessation in humans. The current experiment indicates that the level of smoking behavior prior to cessation may affect the ability of bupropion to increase abstinence rates. For instance, bupropion may be more efficacious for individuals who have a higher rate of smoking, and possibly could be less effective in cessation attempts of smokers who have a lower rate of smoking. This notion is difficult to evaluate based on previously reported clinical trials, as the two main clinical trials attempted to control for cigarette consumption by making groups approximately equal in the number of cigarette smoked per day (Hurt et al., 1997; Jorenby et al., 1999). Further work is needed to establish the importance of rate-dependency when determining whether future compounds will help or hinder smoking cessation attempts in the clinical setting.

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