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EVALUATION REINFORCER MAGNITUDE AND RATE DEPENDENCY OF RESISTANCE TO CHANGE MECHANISMS

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Abstract

In many circumstances, reinforcer magnitude appears to modulate the rate-dependent effects of drugs, such that when schedules arrange for relatively larger reinforcer magnitude, rate dependency is attenuated compared to behavior maintained by smaller magnitudes. The current literature on resistance to change suggests that increased reinforcer density strengthens operant behavior, and such strengthening effects appear to extend to the temporal control of behavior. As rate dependency may be understood as a loss of temporal control, the effects of reinforcer magnitude on rate dependency may be due to increased resistance to disruption of temporally controlled behavior. In the present experiments, pigeons earned different magnitudes of grain during signaled components of a multiple fixed-interval schedule. Three drugs, clonidine, haloperidol, and morphine, were examined: all three decreased overall rates of key pecking; however, only the effects of clonidine were attenuated as reinforcer magnitude increased. An analysis of within-interval performance found rate-dependent effects for clonidine and morphine, but those effects were not modulated by reinforcer magnitude. Additionally, we included prefeeding and extinction conditions, standard tests used to measure resistance to change. In general, rate-decreasing effects of prefeeding and extinction were attenuated by increasing reinforcer magnitudes. Rate-dependent analyses of prefeeding showed rate-dependency following those tests, but in no case were these effects modulated by reinforcer magnitude. The results suggest a resistance-to-change interpretation of the effects of reinforcer magnitude on rate dependency is not viable.

Keywords

clonidine; haloperidol; morphine; rate dependency; reinforcer magnitude; fixed interval; pigeon; key peck

INTRODUCTION

Early observations that drug effects may depend on the baseline rate of schedule-controlled behavior led to a general formulation the rate-dependency concept (Barrett & Bergman, 2008; Dews & Wenger, 1977; Kelleher & Morse, 1968; Knealing & Schaal, 2002). Most

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commonly studied under fixed-interval schedules, where reinforcers are delivered following the first response after a fixed time period elapses, rate dependency reflects the tendency for low response rates to be increased by drugs; relatively high rates are often unaffected or decreased. Although the straightforward nature of rate dependency may be seen as an elegant, unifying principle for understanding and predicting drug effects on schedule-controlled behavior, later research revealed that early findings were not as general as hoped (e.g., Sanger & Blackman, 1976); it appeared that in many situations the circumstances giving rise the baseline response rate were more important than the rate itself. Branch (1984) further noted that an adequate understanding of rate dependency required an understanding of the relevant behavioral processes controlling behavior.

Over the past several years, there have been few additions to our understanding of behavioral variables that determine rate dependency; nevertheless, the data suggests that important environmental variables can be identified. For example, Odum et al. (1998) examined the rate-dependent effects of morphine on behavior maintained by fixed-interval schedules of food delivery under varied levels of food deprivation. Under mild levels of food deprivation ($> 90\%$ free-feeding weight) morphine tended to increase low response rates early in the fixed-interval and, to a smaller extent, reduced the higher rates occurring late in the interval. Increasing deprivation levels further to 70% free-feeding weight enhanced the rate-increasing effect of morphine early in the interval. A rate-dependency analysis showed that food deprivation did not systematically affect the slope of the function, but instead tended to affect the y-intercept, with increasing levels of deprivation increasing the intercept.

More recently, our lab has explored the role of reinforcer magnitude in determining rate-dependent effects observed under multiple fixed-interval schedules. In contrast to the effects of food deprivation, increasing reinforcer magnitude tends to attenuate the steepness of the slope of the function and has not consistently affected the intercept. Collectively, we have shown that reinforcer magnitude modulates rate-dependent effects of a variety of drugs including cocaine, chlordiazepoxide, desipramine, and fluvoxamine (Ginsburg & Lamb, 2008; Lamb & Ginsburg, 2008; Ginsburg et al., 2011), although we have identified some cases where magnitude apparently does not alter rate dependency (e.g. d-amphetamine, Ginsburg et al., 2011).

The relationship between rate dependency and reinforcer magnitude prompts speculation as to a possible behavioral mechanism that might explain the findings. One promising account of the data lies within current theories of resistance to change of operant behavior. Specifically, Nevin and colleagues have shown that the associative relationships embedded in the context of operant contingencies determine the persistence of operant behavior in the face of challenges (e.g., removal of reinforcement). In particular, responding maintained by more frequent or larger magnitude reinforcers is more resistant to change than behavior maintained by less frequent or smaller magnitude reinforcers (Nevin & Grace, 2000; Nevin & Shahan, 2011). In light of such findings, one could conceive of rate dependency as reflecting disruption of the temporal pattern of behavior relative to control patterns following a drug challenge (e.g., Gonzalez & Byrd, 1977). To the degree that temporal pattern of behavior can come under control of the stimulus-reinforcer relationships that

govern resistance to change, patterns maintained by larger reinforcer magnitudes would be expected to be more resistant to disruption, i.e., less rate-dependent, than patterns maintained by smaller reinforcer magnitudes.

The hypothesis that rate dependency is related to resistance to change is made plausible by prior work showing temporal control over behavior does come under control of variables affecting resistance to change. Grace and Nevin (2000) examined the relationship between reinforcer magnitude and temporal control using a peak interval procedure. During peak interval procedures, responding is established on regular FI schedules. Mixed with the regular FI intervals are non-reinforced probe trials (e.g., Church et al. 1994; Kirpatrick-Steger et al. 1996). Performance on probe trials is characterized by an increasing response rates that peak near the time reinforcers are normally collected and then decrease. Grace and Nevin (2000) found that typical tests of resistance to change shifted the peak response rate to earlier points in the interval; increasing reinforcer magnitude, moreover, attenuated the extent of the shift, which led Grace and Nevin to conclude that the resistance of overall response output and temporal control were affected similarly by variables governing resistance to change (see also Odum et al., 2005). Note also that the results on temporal pattern could be conceptualized in terms of a rate-dependent effect. If the peak response rate shifts to an earlier time in the interval, normally lower rates early in the interval would be seen as increased; by the same token, higher rates later in the interval would be decreased, or perhaps unaffected if the peak was not well defined.

In the present experiment, we sought to determine the relationship between resistance to change and rate dependency by examining several drugs and standard tests of resistance to change on both changes in response rate and rate dependency. We studied morphine because it is known to produce rate-dependent effects (e.g., Odum et al., 1998). Haloperidol was included because it is typically without classical rate-dependent effects (Leander, 1975). Clonidine was included because in a previous study we showed its effects on response rate maintained by fixed-ratio schedules were consistent with the predictions based on the resistance-to-change literature (Pinkston et al., 2009). We also examined the rate-dependent effects of standard behavioral tests of resistance to change (e.g., prefeeding and extinction).

METHOD

Subjects

Six male White Carneau pigeons were used in the present study, although not all pigeons participated in each condition. All pigeons had prior experience with the experimental task and all pigeons previously had participated in the acute testing of several other compounds (Ginsburg & Lamb 2008; Lamb & Ginsburg 2008; Ginsburg et al 2011). No pigeon had experienced any drug within 3–4 weeks prior to the tests reported here. Pigeons were housed individually in stainless steel cages. Each pigeon was maintained at 80% of its free-feeding weight for the duration of the study. To maintain body weight, supplemental grain was given post-session as needed. Water and grit were continuously available in the home cage. The colony room was temperature- and humidity-controlled. Lights in the colony room operated on a 12:12 h light:dark cycle. All experimental procedures were approved by the

Institutional Animal Care and Use Committee of the University of Texas Health Science Center at San Antonio.

Apparatus

Experimental sessions were conducted in commercial pigeon chambers (Gerbrands #G7410S, Alderston, MA, USA). One wall of the chamber was constructed of brushed aluminum and served as the intelligence panel. A shielded 24-V lamp mounted on the panel near the ceiling provided general illumination. The panel provided three, horizontally aligned plastic response keys. Only the center key was used in the present study. The key could be transilluminated white, green, or red by 24-V lamps mounted behind the key. Below the center key, a rectangular aperture provided access to a standard diet (Purina Checkers, Purina Mills, St. Louis, MO, USA) delivered to the pigeon via a solenoid-operated food hopper. Access to food was accompanied by illumination of the aperture by a 24-V white lamp. Experimental events and data recording were accomplished by a computer running Med-PC® IV (Med Associates, Georgia, VT, USA).

Procedure

Experimental sessions were conducted Monday-Friday each week. During the session, pigeons worked on a three-component multiple FI 5-min schedule of food delivery. In each component, the first peck to occur after 5 minutes turned off the key light and presented the food hopper. The duration of the hopper presentation was set to 2-, 4-, or 8-s of access for components signaled by the green, white, or red key light, respectively. If available food was not collected within 60s, the food was cancelled and the component terminated. In any case, a 60-s blackout period was programmed between components. During the blackout, no stimuli were presented and responding had no programmed consequences. Sessions consisted of four blocks; during each block, each component was presented in a random order.

Clonidine, morphine, and haloperidol were tested with each pigeon in a mixed order. During drug testing, doses were administered on Tuesdays and Friday. Each dose and the saline vehicle were tested twice. During the first pass through the dose-response function, the order of doses was determined randomly. During the second pass, the order of doses was the reverse order of the first pass. On Thursdays, vehicle was administered and response rates were normalized to those values for data analysis.

At the end of the experiment, we conducted additional tests to measure the persistence of behavior in response to prefeeding and programmed extinction. The order of testing was determined individually for each pigeon. Several weeks elapsed between tests. The prefeeding test was conducted over a single week. On Monday of the week, sessions were conducted as normal. Subsequently, pigeons received 20, 40, 60, and 80 g of food 30 min prior to the daily session on Tuesday, Wednesday, Thursday and Friday, respectively. The extinction test was also conducted over one week. Again, on the Monday of the test, the session was conducted as normal and the data served as the control. For the next three sessions, components ended after 5 minutes regardless of responding; 60-s blackouts still operated between components.

Drugs

Clonidine hydrochloride, haloperidol, and morphine sulfate were purchased from Sigma Chemicals (St. Louis, MO). All drugs were dissolved in saline to yield an injection volume of 1 ml/kg; 2–3 drops of a concentrated lactic acid solution was added to the saline (yielding approximately a 0.002 M lactic acid solution) to help dissolve haloperidol. Dosages given are in terms of the salt for clonidine and morphine and in terms of the free base for haloperidol. Drugs were injected into the pectoral muscle 10 minutes prior to experimental sessions. Site of injection was alternated on successive tests.

Data Analysis

Two primary measures were of interest. Response rate per session was calculated as the number of key pecks emitted under each component divided by the time the component light was illuminated. For the analysis of response rate, absolute rates were divided by their respective control values (vehicle determinations on Thursdays for drug tests and Mondays for extinction and prefeeding tests) and multiplied by 100. To examine functional relationships between potency and grain duration, ED50 values were computed for each pigeon, which were computed by finding the two doses bracketing a 50% reduction of baseline responding. Lines were fit to the identified points using the logarithm of the dose; the dose producing a 50% reduction in responding was then computed via linear interpolation and exponentiating the result.

To quantify changes in the temporal pattern of key pecking, we conducted rate-dependency analyses for each dose tested. For rate dependency analysis, the number of pecks in each 10th of the fixed interval was determined and converted to responses per minute; pecks following the elapse of 5 min were excluded from rate-dependency analyses. The resulting rates were averaged over corresponding determinations within each pigeon on a bin-by-bin basis. Similar calculations were performed on the data from control sessions. Rate-dependency plots were then constructed by plotting the logarithm of the drug rate / control rate *100 against the logarithm of the control rate. Response rates less than 0.01 responses per second were excluded from the calculations because they are statistically unreliable. Separate regression analyses were performed for each pigeon. Regression parameters were then analyzed using repeated-measures ANOVA. We should note that for all ANOVAs presented below, we first conducted analyses including order of drug determination as a factor (first and second administrations). In no case was the main effect of order significant, nor was its interaction with any term significant; hence, data across determinations were averaged for all reported analyses.

RESULTS

Absolute response rates under the FI 5-min schedule during control sessions ranged from an average of 0.3 – 1.0 responses / s (2-s component), 0.2 – 1.2 responses / s (4-s component), and 0.3 – 1.3 responses / s (8-s component) across pigeons. Repeated-measures ANOVA found no significant differences in response rates as a function of grain duration.

Figure 1 shows the effects of clonidine, haloperidol and morphine on overall response rate expressed as a percent of control values (i.e., vehicle determinations made each Thursday). In the case of clonidine, there was apparent attenuation of the decreasing effects on response rate, but only when behavior was maintained by 8-s presentations of grain. However, the rate-decreasing effects of haloperidol and morphine were not affected by grain duration. Across animals, the average ED50 for clonidine was 0.011, 0.010, and 0.015 mg/kg for the 2-, 4-, and 8-s duration of grain presentation, respectively. The respective values for haloperidol were 0.010, 0.082, and 0.011 mg/kg and for morphine 1.51, 1.43, and 1.42 mg/kg. A repeated-measures ANOVA on the ED50s identified a significant effect of grain duration for clonidine ($F(2,8) = 8.7$, $p < .01$) and post-hoc comparisons showed that values under both the 2-s and 4-s grain durations were reduced compared to the 8-s duration ($p < .05$ in both cases); the ED50 values for 2-s and 4-s, however, were not statistically different. Similar analyses for haloperidol and morphine found no significant relationship between grain duration and ED50 values.

As outlined above, we conducted rate-dependency analyses to examine how the temporal pattern of behavior changed over the interval. In general, if a drug did not alter the temporal pattern of responding, data obtained following drug administration would be equivalent to control data and regression slopes would be equivalent to zero (a horizontal flat line); rate-dependency would be reflected by slopes with negative values. More specifically, if reinforcer magnitude attenuated rate-dependent effects, we would expect to see an inverse relationship between slope and grain duration. Changes in the y-intercept indicate how responding changes when control rates are equal to 1 response / s; in our data, such data reflect level shifts in responding near the last third of the fixed interval.

As can be seen in Table 1, haloperidol did not produce rate-dependent effects, but both clonidine and morphine did. In neither case, however, was there any indication that these rate-dependent effects were modified by grain duration. The slopes and intercepts from each individual regression were analyzed by two-way repeated-measures ANOVA (Dose X Grain Duration). For clonidine, data from the 0.056 mg/kg dose was excluded because only 3 pigeons provided sufficient data for the calculation of the regression; the remaining two pigeons only emitted a few pecks scattered over the session. ANOVA showed a significant effect of clonidine dose on slope of the regressions ($F(3,24) = 4.6$, $p < .01$) and intercepts ($F(3,24) = 4.9$, $p < .01$); there was no significant effect of grain duration nor its interaction with dose for either measure. Figure 2 provides some illustrative data from individual animals. Note, that the data in Figure 2 show the relationship between two dependent variables, and in this important way, the data differ from other figures; though the analyses do permit a description of how temporal control changed with respect to baseline responding, they do not allow us to interpret causal relationships between baseline rate and drug effects. Still, the data show that there was a tendency for low rates early in the interval to be increased, and higher rates near the end of the interval to be decreased, but the slopes of the regression lines were not related to grain duration.

As has been reported previously, morphine produced rate-dependent effects, and, as in the case of clonidine, increasing the dose tended to decrease the slope and reduce the intercept. Repeated-measures ANOVA, excluding the 5.6 mg/kg dose because insufficient pecks were

obtained from two pigeons, reveal significant main effects of dose on slope ($F(3,24) = 20.1$, $p < .001$) and intercept ($F(3,24) = 4.5$, $p < .025$), but these effects did not vary with the duration of grain presentations. Representative data from individual pigeons are shown in Figure 2 for the 3.2 mg/kg dose of morphine. The data show that morphine both increased low rates early in the interval and decreased higher rates at the end of the interval. Rate-dependency, however, was not modulated by grain duration.

Finally, we assessed resistance to change following prefeeding and extinction. The results are shown in Figure 3. On average, the pattern of results following prefeeding is consistent with results reported in the literature; however, the data were quite noisy across pigeons. A two-way repeated-measures ANOVA found no significant effect of either prefeeding amount or duration of grain access, nor a significant interaction term, although the effect of prefeeding amount approached significance ($p = 0.07$). Under extinction, response rates decreased more rapidly when behavior was maintained by shorter durations of grain access. Two-way repeated measures ANOVA identified a significant effect of extinction day ($F(2,16) = 43.5$, $p < .001$) and grain duration ($F(2,16) = 4.5$, $p < .05$); importantly, there was also a significant interaction between extinction day and grain access duration ($F(4,16) = 3.6$, $p < .05$).

To determine a possible relationship between resistance to change and rate-dependency, we also conducted rate-dependent analyses of the extinction and prefeeding data. Mean data are shown in Table 2. Only data from the prefeeding condition are shown, as in the case of extinction there was no evidence of rate-dependency for any pigeon and none of the regression slopes differed from zero. In general, prefeeding, but not extinction, appeared to have rate-dependent effects, but there was no general effect of reinforcer magnitude on either slopes or intercepts.

DISCUSSION

Previous work in our lab has shown rate-dependent drug effects can be modulated by reinforcer magnitude; in general, manipulations that attenuate rate-dependent effects are similar to those that increase resistance to change of operant behavior (Nevin & Grace, 2000). Additionally, Grace and Nevin (2000) showed that associative relationships determining resistance to change of overall responding may extend to the temporal organization of behavior. Given that rate dependency may be understood as a loss of temporal organization in schedule-controlled behavior, and our general procedures are similar to those used to examine resistance to change, a resistance-to-change interpretation presents itself as an attractive account for our findings. Yet, the present study did not support the hypothesis that reinforcer magnitude effects on rate dependency are related to resistance to change.

One important consideration in interpreting our results concerns the relationship between obtained reinforcer density and programmed reinforcer density. If pigeons were not consuming all of the food earned, the experiment may not have promoted clear conditions for assessing resistance to change. Although we did not measure the time spent eating for each reinforcer, we did measure the number of times the pigeons encountered the limited

hold contingency. Recall, if the pigeon did not collect an earned reinforcer within 60s, the reinforcer was canceled and schedule advanced to the next interval. Under non-drug conditions, pigeons never encountered the limited hold. During drug testing, reinforcer omissions were observed to be a roughly all-or-none phenomenon, that is, pigeons generally either produced all 4, or perhaps 3, reinforcers available from each component; at the highest doses, however, when pecking was maximally reduced, it was typical for pigeons to earn zero or one reinforcer per component. Analyses of the pattern of reinforcer omissions did not suggest shorter (or longer) grain durations were differentially affected, nor were omissions differentially affected by the particular drug tested. Finally, we should note that the experimental conditions were sufficient to observe differences consistent with the literature on resistance to change, in terms of the effects of clonidine and extinction on response rate, indicating that our procedure could reproduce previous findings.

In terms of overall responding, the effects of haloperidol and morphine were not altered by reinforcer magnitude, but the effects of clonidine were. Previously, we showed that the rate-decreasing effects of clonidine on behavior maintained by FR schedules were attenuated by increasing reinforcer magnitude (Pinkston et al., 2009). So, it would seem the magnitude effect on overall output is a stable feature of the behavioral effects of clonidine. The interactions between the effects of clonidine on response rate and reinforcer magnitude may have to do with its effects on attention-related processes. Impaired attention has been one account for why drug effects may fail to correspond to predictions of resistance to change theories (e.g., Harper, 1999). Clonidine, however, may enhance stimulus control and attention (Brown et al., 2012; Franowicz & Arnsten, 1999; Schneider et al., 2010), and those effects have contributed to its recent approval for the treatment of Attention-Deficit/Hyperactivity Disorder (e.g., Sallee et al., 2013). The fact that we have observed the magnitude effect on overall response measures across two different procedures with clonidine suggests future studies using our preparation with adrenergic agonists are important and could potentially lead to a new behavioral assay for assessing cognitive enhancement.

Both clonidine and morphine produced rate-dependent effects during the fixed-interval. Additionally, rate-dependency analysis of typical behavioral tests of resistance to change found that the effects of prefeeding, but not extinction, were rate-dependent. In no case, however, were rate-dependent effects related to reinforcer magnitude, despite the fact that reinforcer magnitude did modulate the effects of clonidine and extinction on overall measures of response rate. Collectively, the data suggest a dissociation between the effects of reinforcer magnitude on overall response rate and rate dependency. So, although research on resistance to change has provided important principles for interpreting drug effects on behavior in some cases (Nevin & Grace, 2000; Poling et al., 2000; Harper, 1999), it does not appear to provide an organizing framework for understanding how reinforcer magnitude affects the rate-altering and rate-dependent effects of drugs on fixed-interval schedules (see also Cohen, 1986; Ginsburg et al., 2011).

The finding that the effects of reinforcer magnitude on response rate and rate dependency do not covary stands at odds with the findings of Grace and Nevin (2000) using the peak interval procedure. It is possible that rate dependency is not related to temporal control in

the same way as the peak interval procedure. Grace and Nevin, for example, indicated that response rates nearest to the end of the interval (peak response rates) were more sensitive as a measure of resistance to change than measures comprising the entire interval. Rate-dependency computations are based on data from the entire fixed interval, so perhaps as a measure of temporal pattern they tap into multiple sources of control, resistance to change being only one. An important area for future research will be to compare rate-dependency analyses with more traditional measures of temporal control. Such investigations would be worthwhile as they stand to advance our knowledge of the behavioral processes at work in rate-dependent effects as a general description of drug action.

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Figure 1.

Rate-decreasing effects of clonidine, haloperidol, and morphine. The y-axis plots the response rate as a percentage of control against dose on the x-axis. Note that the axes are logarithmically spaced. Error bars on control points represent 95% confidence intervals.

Figure 2.

Individual data for selected doses of clonidine and morphine. The y-axis plots log (drug rate / control rate * 100) by log (control rate) in responses per second on the x-axis. The results of two doses are arranged by columns; individual data from each pigeon are shown in rows. Note that different pigeons contributed to the data in the second row. Data from the component providing 2-s, 4-s, or 8-s access to grain are shown for by open circles, triangle, and squares, respectively. Best fitting regression lines for the 2-s, 4-s, or 8-s conditions are shown by the solid, short dash, and dotted lines, respectively. The horizontal line on the vertical axis at 2 indicates the line of no effect.

Figure 3.

Tests of prefeeding and extinction. The y-axis plots the response rate as a percentage of control against amount prefed prior to the session (g) in the upper graph and day of extinction on the lower graph. Note that the y-axis is logarithmically spaced.

Table 1

Rate-dependency analysis for clonidine, haloperidol, and morphine showing slopes, intercepts, and 95% confidence intervals. Bold values indicate slopes significantly different from zero or intercepts significantly different from log(100).

	SLOPE			INTERCEPT		
	2 s	4 s	8 s	2 s	4 s	8 s
Clonidine						
Dose (mg/kg)						
0.0056	-0.03 (-0.29, 0.23)	0.08 (-0.13, 0.29)	-0.37 (-0.66, -0.08)	2.01 (1.64, 2.38)	2.02 (1.91, 2.13)	2.13 (1.92, 2.13)
0.0100	-0.48 (-0.74, -0.22)	-0.45 (0.75, -0.15)	-0.56 (-0.75, -0.37)	1.64 (1.37, 1.91)	1.60 (1.35, 1.85)	1.85 (1.68, 2.02)
0.0180	-0.87 (-1.08, -0.66)	-0.92 (-1.55, -0.29)	-0.83 (-1.07, -0.59)	0.94 (0.25, 1.55)	1.21 (0.84, 1.58)	0.76 (0.84, 1.58)
0.0320	-0.72 (-1.02, -0.42)	-0.95 (-1.58, -0.32)	-1.40 (-1.84, -0.96)	1.01 (0.34, 1.72)	0.71 (-0.11, 1.52)	1.89 (1.31, 2.47)
0.0560	-0.96 (-1.13, -0.79)	-1.32 (-1.49, -1.15)	-0.51 (-1.14, 0.12)	0.68 (0.29, 1.07)	0.47 (0.07, 0.87)	1.16 (0.79, 1.53)
Haloperidol						
Dose (mg/kg)						
0.010	0.11 (-0.35, 0.57)	0.09 (-0.32, 0.52)	0.20 (-0.25, 0.65)	1.64 (1.25, 2.03)	1.68 (1.31, 2.05)	1.76 (1.43, 2.09)
0.032	-0.10 (-0.35, 0.57)	0.18 (-0.32, 0.52)	0.13 (-0.25, 0.65)	1.79 (1.58, 2.00)	1.75 (1.31, 2.05)	1.84 (1.43, 2.09)
0.100	-0.14 (-0.25, 0.05)	-0.31 (-0.38, 0.74)	0.15 (-0.22, 0.48)	1.79 (1.58, 2.00)	1.75 (1.54, 1.96)	1.84 (1.73, 1.95)
0.320	-0.17 (-0.35, 0.07)	0.19 (-0.27, 0.65)	0.17 (-0.01, 0.35)	1.65 (1.48, 1.82)	1.64 (1.45, 1.83)	1.74 (1.57, 1.91)
1.000	-0.59 (-0.74, -0.44)	-0.53 (-0.79, -0.27)	-0.44 (-0.73, -0.15)	0.79 (0.40, 1.18)	0.93 (0.69, 1.17)	0.56 (0.06, 1.06)
Morphine						
Dose (mg/kg)						
0.56	-0.07 (-0.29, 0.15)	-0.10 (-0.31, 0.11)	-0.06 (-0.59, 0.47)	1.92 (1.85, 2.00)	1.91 (1.78, 2.04)	1.77 (1.41, 2.14)
1.00	-0.45 (-0.70, -0.20)	-0.34 (-0.66, -0.02)	-0.39 (-0.54, -0.24)	1.76 (1.34, 2.18)	1.69 (1.34, 2.18)	1.89 (1.68, 2.21)
3.20	-0.66 (-0.78, -0.54)	-0.72 (-0.95, -0.49)	-0.73 (-0.98, -0.48)	1.05 (0.35, 1.75)	1.05 (0.62, 1.91)	1.26 (0.62, 1.91)
5.60	-0.75 (-1.11, -0.39)	-0.89 (-1.26, -0.52)	-0.81 (-1.14, -0.48)	0.31 (-0.27, 0.87)	0.31 (-0.26, 0.88)	0.31 (-0.27, 0.89)

Table 2

Rate-dependency analysis of prefeeding tests showing slopes, intercepts, and 95% confidence intervals. Bold values indicate slopes significantly different from zero or intercepts significantly different from log(100).

Prefeeding (g)	SLOPE		INTERCEPT	
	2 s	4 s	2 s	4 s
20	-0.64 (-0.83, -0.45)	-0.56 (-0.78, -0.33)	-0.50 (-0.72, -0.28)	1.74 (1.46, 2.02)
40	-0.52 (-0.69, -0.36)	-0.24 (-0.64, 0.15)	-0.42 (-0.84, -0.02)	1.60 (1.33, 1.87)
60	-0.72 (-0.81, -0.62)	-0.26 (-0.75, 0.23)	1.09 (0.66, 1.52)	1.28 (0.77, 1.80)
80	-0.84 (-1.14, -0.54)	-0.33 (-0.51, -0.15)	0.74 (0.37, 1.11)	0.95 (0.82, 1.18)