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Effects of quinpirole on operant conditioning: perseveration of behavioral components

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Abstract

Quinpirole (QNP) is reported to elicit repetitive spontaneous behaviors as well as reduce extinction of operant responses. To determine whether these effects represent perseveration of learned behaviors, behavioral components were examined during the acquisition and extinction of operant responses. Rats, receiving either 0, 0.08, or 0.60 mg/kg QNP were trained to nose poke to receive water. The lower dose interfered with acquisition, but once learned, behavioral characteristics were normal. The higher dose produced excessive time in the drinking well when water was delivered. When water was withheld, the control and 0.08 mg/kg dose groups altered their behavior by initially increasing nose poke duration, followed by a progressive extinction of the operant response. The higher dose group, however, did not modify the characteristics of their behaviors, but continued to perform the behavioral sequence in the absence of reward. These effects are not ascribable to generalized locomotor activation in that response rates during reinforced responses, as well as at the beginning of the extinction phase, did not differ significantly across treatment groups. These results indicate that perseveration effects of QNP are not accountable by general behavioral arousal, nor are specific to extinction. Instead, these effects appear to reflect reduced adaptability of learned behavioral patterns to changes in reinforcement contingencies.
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1. Introduction

Dopamine plays a fundamental role in operant responses [3,27,31], contributing to multiple neural mechanisms mediating motoric as well as reinforcement components of behavior. Reduced dopaminergic activity disrupts components of operant conditioning, including disrupted response acquisition [47,51], as well as reduced responding for primary reinforcement [1,7,22,23,25,26,28,34,37,38,41,42]. Response reduction produced by dopamine receptor antagonists resembles extinction produced by non-reinforcement [2,16], although differences in response patterns exist [4,14,48]. Compared to periods of non-reinforcement, dopamine depletion produced less within-session response decline, and greater inter-response pause length [33,34].

Alternatively, activation of dopamine receptors is associated with stereotyped behaviors [5,15,20] and perseveration [18,30,36]. Among reports of the production of perseverative behaviors are those examining activation of D_2 dopamine receptors. Specifically, systemic administration of quinpirole (QNP), a dopamine D_2 receptor family agonist, produces stereotypy, including repetitive oral behaviors, such as mouthing, sniffing, and licking [8,17,35,44], as well as locomotor stereotypy in which rats repeatedly travel along routes confined to a limited area [6,9,10,44]. Chronic QNP treatment also causes reduced behavioral variability, which is characteristic of perseveration. Rats that navigated a T-maze to locate a food reward demonstrated reduced spontaneous alteration behavior [12].

Repetitive behaviors and reduced behavioral variability produced by QNP represent perseveration, in which behaviors are maintained regardless of whether they are effective or appropriate. Consistent with these effects, QNP is reported to reduce the rate of behavioral extinction, thereby maintaining behavior in the absence of reinforcement [21]. In this study, rats trained to nose poke for water reinforcement demonstrated a significant reduction in the rate of extinction during a period of non-reinforcement when treated

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with QNP. This reduced extinction effect may result from QNP interfering with signals associated with the omission of a predicted reinforcer. Reduction or omission of predicted reinforcers is associated with a phasic decrease in tonic dopamine activity [39]. The agonist effect of QNP may serve to counteract dopamine activity reduction, and thereby interfere with subsequent behaviors made in response to changes in reinforcement contingencies.

The study reported here was performed to further investigate the role of QNP on the acquisition and extinction of operant behaviors. Based upon previous reports, it appears that QNP's effect on operant conditioning is not specific to processes active during extinction, but also includes perseveration of other behavioral components. It is hypothesized that characteristics of both the operant response and the consummatory behavior will be less affected by changes in reinforcement contingencies in QNP treated rats than in control animals. Specifically, it is predicted that in addition to a higher rate of responding during non-reinforcement, QNP treated rats will also show perseveration of the consummatory behavior on each trial, as well as less change in the duration of the operant response, consummatory behavior, and inter-response interval during non-reinforcement. To test this prediction, persistence of these behavioral components were compared among drug treatment groups during the acquisition, maintenance, and extinction of an operant response.

2. Materials and methods

2.1. Subjects

Fifteen Long–Evans rats (Charles River Breeding Laboratory), at 104–146 days of age, served as subjects. Animals were housed in a temperature-controlled facility that was maintained on a 12-h light:12-h dark cycle.

2.2. Apparatus

Behavioral measurements were made in an operant conditioning chamber (Fig. 1A) that contained a front panel on which an opening led to a glass funnel. The outer section of the funnel was positioned between an infra-red (I/R) emitter-detector pair. Head placement within the funnel interrupted the I/R beam, which was detected by computer. Six centimeter to the left of the funnel opening was a well that contained a drinking spout. The drinking spout was positioned on the bottom of the well, centered 7 mm inside the opening. A second I/R pair was positioned above the drinking spout which was used to detect the presence of the rat's head within the well (Fig. 1B,1C). A measured amount of water (approximately 0.04 ml) could be delivered by means of a solenoid driven valve that was mounted on the side of the chamber. Circuitry for the I/R pairs and the solenoid were interfaced via solid-state relay switches to a computer. Reward delivery and data collection were controlled by computer.
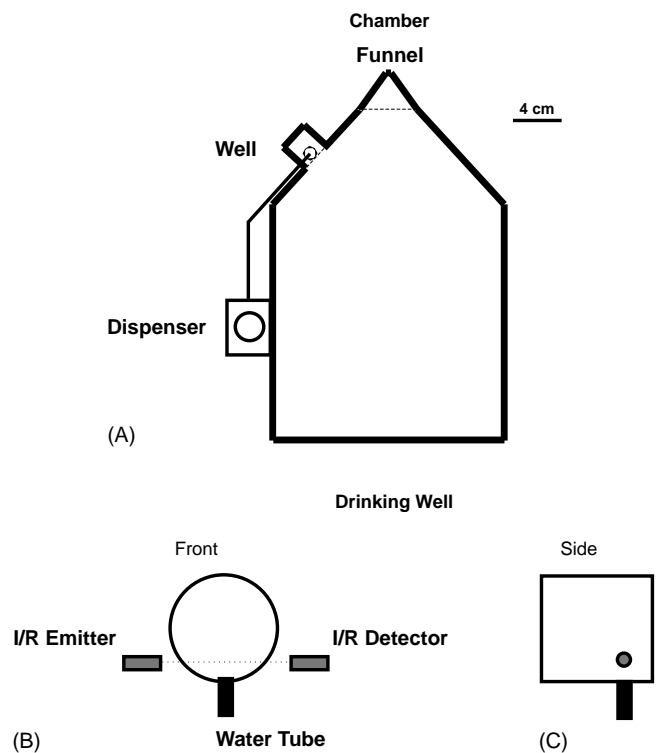

Fig. 1. (A) Top view of experimental chamber. Rats were conditioned to enter the funnel in order to trigger release of water to the well. (B) Front view of drinking well. Water was delivered from the bottom of the well. Head placement within the entrance of the well interrupted an infrared emitter/detector pair. (C) Side view of the drinking well. Rats entered well from the right.

2.3. Procedure

For each day of testing, including magazine training, rats were water deprived for 22.5 h. Rats received water during experimental sessions, contingent upon their behavior, and then receive water ad libitum in their home cages for 1 h after each session. Sessions were held once per day for 6 consecutive days.

2.3.1. Magazine training
All rats initially underwent magazine training for one session of 15 min in which they were introduced into the chamber to become familiar with reward delivery. During magazine training, water was delivered on a random schedule, averaging twice per minute, for a total of 30 rewards.

2.3.2. Conditioning
Following magazine training, rats were conditioned with a free-operant procedure with continuous reinforcement to place their heads within the funnel in order to trigger delivery of water from the drinking spout within the well. A single response is defined as the behavioral sequence of entering the funnel, followed by entering the drinking well. Training was considered complete when rats completed 75 responses. The time at which each response occurred was recorded

throughout the session. For each of 4 days, rats remained in the chamber until 75 responses (±5) were initiated. In this regard, all rats performed approximately the same number of responses and received the same amount of reinforcement on each of the first 4 days of conditioning. The time at which the operant response was initiated, and the amount of time spent within the funnel and the drinking well, were recorded throughout the session. For behaviors in which rats removed their head from the funnel, and then returned to the funnel before entering the well, the total time spent in the funnel was recorded. Similarly, for behaviors in which rats repeatedly entered the drinking well before returning to the funnel, the total time spent in the well was recorded.

2.3.3. Extinction

On the day following the fourth conditioning session, rats were placed into the chamber, but reward delivery was withheld (solenoid was disabled). Responses continued to be tracked throughout the session. On this final day of testing, rats remained in the chamber for at least 90 min, or until responses ceased.

2.4. Treatment groups

Rats were randomly assigned to one of three treatment groups in which they received either sterile saline (control group), 0.08 mg/kg quinpirole (QNP) hydrochloride (Sigma-Aldrich) (dissolved in saline), or 0.60 mg/kg QNP, delivered i.p. 1 h before every sessions. Each rat was assigned to one group and thereby received the same drug treatment for all phases of testing.

3. Results

Four behavioral measurements were recorded: time in the funnel (operant response), time in the drinking well (consummatory behavior), inter-response duration, and number of responses to extinction during non-reinforcement. Characteristics of the initial acquisition were examined by comparing the first and last 10 responses made on the first day of conditioning.

3.1. Acquisition

All rats in the control and 0.60 mg/kg dose groups acquired the conditioned behavior within the first session, completing 75 responses (±5) within 23.9–83.3 min. However, acquisition was significantly disrupted for the 0.08 mg/kg dose group. For six of seven rats in this group, fewer than 10 responses were initiated in 90 min. These animals were therefore returned to their home cages for 20 min, and then returned to the test chamber. Two of these rats then completed 75 responses. For the remaining animals, training was attempted again the following day. One of these animals acquired the behavior in the first session of the second

day, and a second animal did so in a second session. The remaining two animals received no further training. Therefore, data was acquired for five of seven rats assigned to the 0.08 mg/kg dose group, four of whom required multiple sessions to complete 75 responses. To best accommodate the delayed acquisition of the 0.08 mg/kg dose group, measurements corresponding to day 1 for this group represent the first 75 responses collected across multiple sessions, and inter-response duration was based on time to the last response.
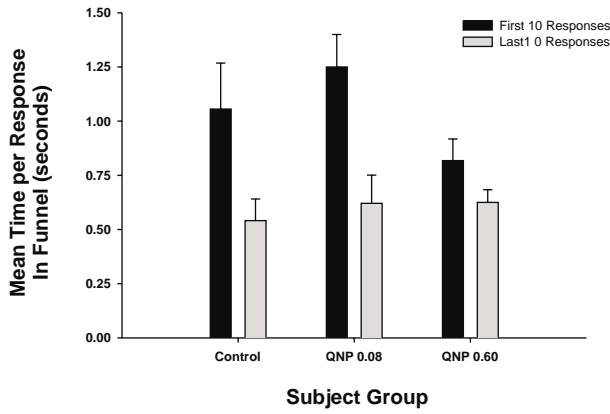
3.2. Time in funnel

Comparing the first and last 10 responses on the first day of training (Fig. 2A), an ANOVA indicated a significant main effect of session segment ($F(1,12) = 29.73$, $P < 0.01$), indicating that more time was spent in the funnel at the beginning of the session than at the end. The main effect of subject group, and the interaction of group by session segment ($F(2,12) = 2.57$, $P = 0.118$) was not significant, indicating that drug treatment had no effect on time in the funnel on the first day of training.

Mean time in the funnel was then examined across days, including the fifth day in which reward was withheld (Fig. 2B). ANOVA indicated a significant main effect of subject group ($F(2,12) = 8.33$, $P < 0.05$), a significant main effect of day ($F(4,48) = 43.62$, $P < 0.01$), and a significant interaction of group by day ($F(8,48) = 8.93$, $P < 0.01$). To interpret the interaction, a Tukey HSD test was performed to compare subject groups for each day. Significant differences were found between the control and 0.08 mg/kg dose group on days 3 and 4 (HDS = 0.152 and 0.212, respectively, $P < 0.05$), in which treated animals spent less time in the funnel. Significant differences were also found between the 0.60 mg/kg dose group and the other two groups on day 5 (HSD = 2.605, $P < 0.01$). Examining each group separately across days, for the control and 0.08 mg/kg dose groups, day 5 differed significantly from all other days (HSD = 0.720 and 1.271, respectively, $P < 0.05$), whereas no significant differences were found between pairs of days for the 0.60 mg/kg dose group. These results indicate that the time in the funnel for all groups remained approximately the same for days in which reward was given (between 0.31 and 0.87 s), whereas on day 5 (no reward) the time in the funnel increased to 3.35 and 3.43 s for the control and 0.08 mg/kg dose groups, respectively, whereas the 0.60 mg/kg dose group did not change significantly.
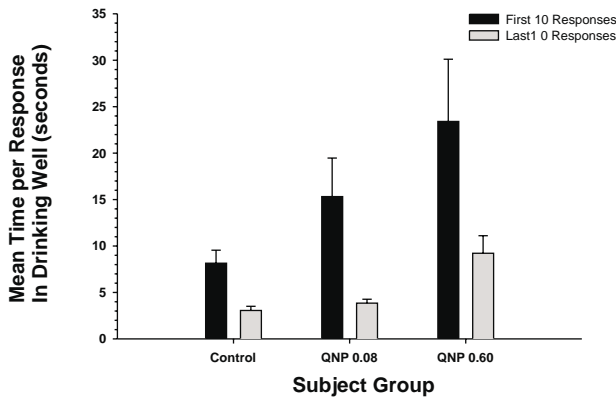
3.3. Time in drinking well

Time spent in the drinking well was compared between the first and last 10 responses of day 1 (Fig. 2C). The main effect of session segment was significant ($F(1,12) = 17.38$, $P < 0.01$), indicating that more time was spent in the well at the beginning of the session than at the end. The main effect of subject group was significant ($F(2,12) = 4.31$, $P < 0.05$),
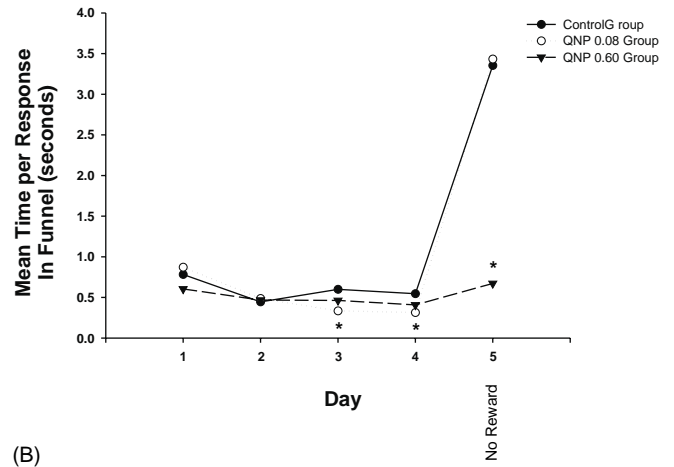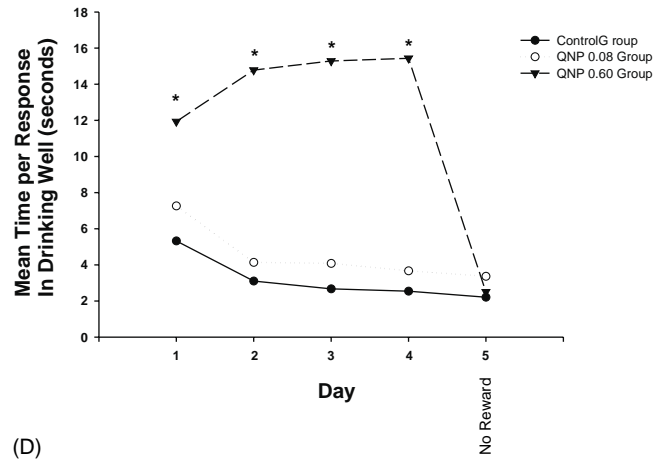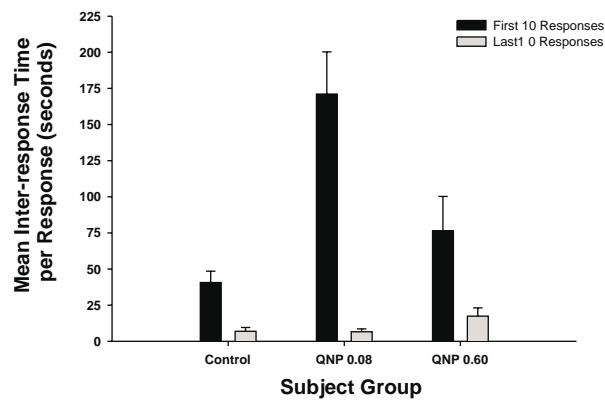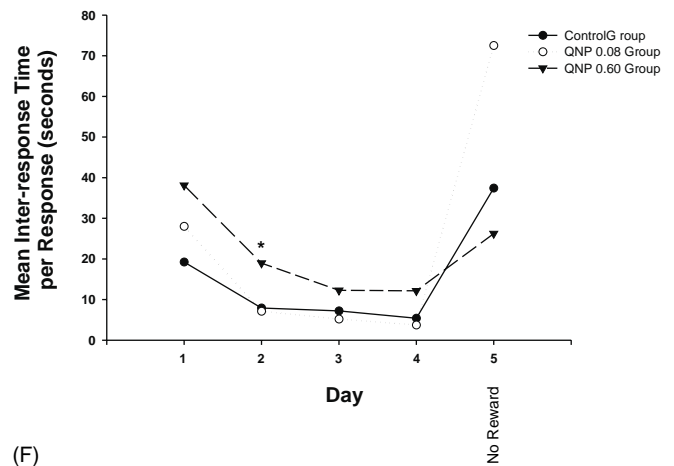
Fig. 2. Mean durations per response of behavioral components for each subject group. Error bars represent S.E.M. and asterisks indicate a significant difference among subject groups (based upon ANOVA, $P < 0.05$). (A) Time in funnel (operant response) for the first and last 10 responses of day 1. (B) Time in funnel across each day of testing. (C) Time in drinking well (consummatory behavior) for the first and last 10 responses of day 1. (D) Time in drinking well across each day of testing. (E) Inter-response duration for the first and last 10 responses of day 1. Measurements are time between consecutive operant responses minus the time spent in the funnel and well. This measurement indexes rate of responding without inclusion of perseveration associated with the operant and consummatory behaviors. (F) Inter-response duration across each day of testing.

whereas the group by session segment interaction was not. Post hoc analysis indicated a significant difference between the control and 0.60 mg/kg dose group (Fischer LSD, $P < 0.05$), whereas no other group differences occurred.

Time spent in the drinking well was then compared across days (Fig. 2D). The main effect of subject group was significant ($F(2,12) = 28.09$, $P < 0.01$), as was the main effect of day ($F(4,48) = 11.47$, $P < 0.01$) and the interaction of group by day ($F(8,48) = 7.86$, $P < 0.01$). Post hoc analyses indicated that for day 1, the 0.60 mg/kg dose group differed from the control group (HSD = 5.405, $P < 0.05$), whereas other group pairs did not differ significantly. For days 2, 3, and 4, the 0.60 mg/kg dose group differed from the other two groups (HSD = 6.766, 8.719, and 6.084, respectively; $P < 0.01$), whereas the control and 0.08 mg/kg dose groups did not differ. On day 5 (no reward), no significant differences were found among groups. Examining each group separately across days, for the control and 0.08 mg/kg dose groups, the time in the well on day 1 was significantly longer than all other days (HSD = 1.043 and 2.491, respectively, $P < 0.05$), whereas no other pair of days differed significantly. For the 0.60 mg/kg dose group, time in the well on day 5 was significantly shorter than any other day (HSD = 8.595, $P < 0.01$), whereas no other pairs of days differed significantly. These results indicate that the 0.08 mg/kg dose group did not differ from the control group, and in both cases the time in the well decreased after the first day, then remained stable, even when reward was withheld. Alternatively, the 0.60 mg/kg dose group remained in the well longer on all days in which reward was delivered. However, when reward was withheld, the time in the well decreased to that of the other two groups.

3.4. Inter-response duration

Inter-response duration is defined as the mean duration between consecutive operant responses minus the time spent in the funnel and well. Inter-response duration was used to index response rate without including perseveration associated with the operant and consummatory behaviors. Comparing the first and last 10 responses of the first day of training (Fig. 2E), a significant main effect of session segment occurred ($F(1,12) = 54.54$, $P < 0.01$), with greater inter-response time at the beginning of the session than at the end. A significant main effect of subject group also occurred ($F(2,12) = 7.867$, $P < 0.01$), as well as a significant interaction between group and session segment ($F(2,12) = 11.04$, $P < 0.01$). Post hoc analyses indicated that for the first 10 responses, the 0.08 mg/kg dose differed from the control and 0.60 mg/kg dose groups (HSD = 80.12, $P < 0.05$), whereas no other group differences were found. For the last 10 responses, subject groups did not differ significantly. These results indicate that the 0.08 mg/kg dose group required significantly longer time than controls to acquire the behavior, but once acquired, this group performed at a normal rate.

Examining inter-response duration across days (Fig. 2F), the main effect of subject group was not significant, whereas the main effect of day ($F(4,48) = 34.96$, $P < 0.01$) and the interaction of subject group by day was significant ($F(8,48) = 7.08$, $P < 0.01$). Examining group differences on each day separately, no differences were found on days 1 and 3, whereas the 0.60 mg/kg dose group differed from the other groups on day 2 (HSD = 11.01, $P < 0.05$), and the 0.60 and 0.08 mg/kg dose groups differed on day 4 (HSD = 6.54, $P < 0.05$). On day 5 (no reward), the 0.08 and 0.60 mg/kg dose groups differed (HSD = 35.85, $P < 0.05$), whereas no other group differences occurred on that day. These results indicate that the 0.60 mg/kg dose group responded with longer inter-response durations than the control group on 1 of the 4 days in which water was delivered, but not on the day reward was withheld. Also, the 0.08 mg/kg dose group did not differ from the control group on days in which reward was delivered, but increased their inter-response duration relative to the 0.60 mg/kg group when reward was withheld.

3.5. Extinction

On day 5 (no reward) the rate of responding progressively diminished until the operant behavior ceased. The criterion for extinction was defined as a lack of responding for 6 consecutive minutes. Number of responses to extinction is defined as the number of complete responses (i.e., entering the funnel followed by entering the drinking well) before reaching the extinction criterion. Comparing the number of responses until extinction (Fig. 3A), subject groups differed significantly ($F(2,12) = 10.46$, $P < 0.01$). Post hoc analysis indicated that the 0.60 mg/kg dose group made significantly more responses than the control and 0.08 mg/kg dose groups (HSD = 205.8, $P < 0.05$).

In order to gain a finer description the extinction process, number of responses for each 4 min interval was tracked throughout the session (Fig. 3B). The control and 0.08 mg/kg dose groups, which extinguished behavior at a mean of 38.3 and 15.4 min, respectively, were tracked for 88 min, whereas the 0.60 mg/kg dose group, which extinguished behavior at a mean of 144.6 min, was tracked for 180 min. A two-way (subject group × time) ANOVA, with repeated measures on the time factor to 88 min, indicated a main effect of subject group ($F(2,12) = 8.42$, $P < 0.01$), a main effect of time ($F(21,252) = 7.92$, $P < 0.01$), and a group by time interaction ($F(42,252) = 2.57$, $P < 0.01$). Post hoc comparisons at each interval indicated that the control and 0.08 mg/kg dose groups did not differ significantly at any time interval, whereas the 0.60 mg/kg dose group responded with a significantly higher number of responses at the 14, 22, 30–50, 62, and 70–86 min intervals.

Maintenance of the operant behavior during non-reinforcement was not specific to entering the funnel. A single response represented the sequence of entering the funnel followed by entering the well. If an animal had repeatedly entered the funnel without attempting to collect water, the
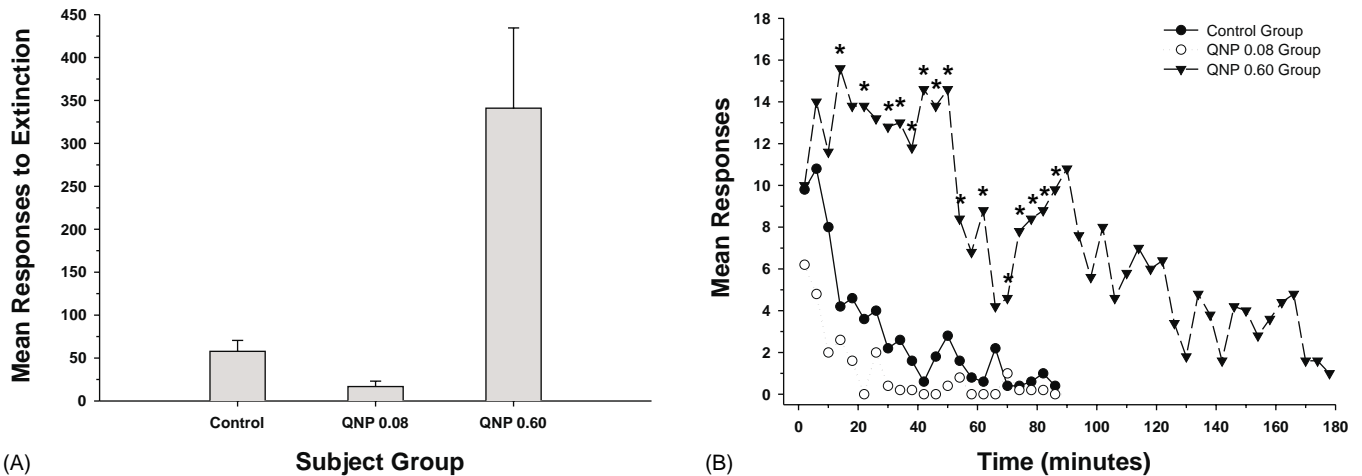
Fig. 3. Performance across subject groups on day 5 (water withheld). (A) Mean number of responses to extinction. (B) Mean number of responses per 4 min intervals across session. Asterisks indicate significant increase in responses by the 0.60 mg/kg dose group (based upon ANOVA, $P < 0.05$).

total duration of time in the funnel for that response would have been inflated. This was not the case, and in fact the 0.60 mg/kg dose group spent the same amount of time in the funnel during non-reinforcement as when water was delivered. Therefore, maintenance of the response during non-reward does not represent a type of compulsive checking, but instead reflects maintenance of the entire sequence operant–consummatory behavioral sequence.

4. Discussion

During the course of operant conditioning and extinction, QNP produced perseveration of several behavioral components. The 0.60 mg/kg dose group spent excessive time in the drinking well when reinforcement was present, increasing to six times the duration of the control group by the fourth day. When reinforcement was withheld, the 0.60 mg/kg dose group did not alter their behavior by increasing time in funnel, as did the other two groups. Instead, this group maintained operant responding, and thereby reduced the rate of extinction. In addition, following acquisition, response rates during reinforced responses, as well as at the beginning of the extinction phase, did not differ significantly across treatment groups. Therefore, behavioral changes described here are not ascribable to locomotor stimulant effects. These results support the hypothesis that QNP produces perseveration of components of learned behaviors, and that these effects do not reflect generalized behavioral arousal, and are not specific to processes only engage during extinction. Instead, the duration of the consummatory behavior is expanded during reward delivery, and the characteristics of the operant response, including duration of the operant behavior and duration of inter-response interval, show less change during non-reinforcement in QNP treated rats.

Excessive time in the drinking well following water delivery reflects a maintenance of behavior presumably beyond

the point that water was consumed. This perseverative effect may reflect exaggerated drinking or licking when water is presented. Excessive snout contact, licking, and mouthing have been observed in QNP treated rats [11,17,43]. Analysis of the microstructure of licking behavior may determine whether QNP impacts the pattern of licking during drinking, which is associated with manipulation of dopaminergic action [40].

During non-reinforcement, the control and 0.08 mg/kg dose groups increased time in the funnel. This change in behavioral pattern was produced in response to changes in reinforcement contingencies, possibly reflecting greater effort made towards the operant behavior that previously elicited reward. This effect did not occur with the 0.60 mg/kg dose group, which again reflects reduced adaptability of a learned behavioral pattern to changing conditions.

A major effect elicited by QNP was the maintenance of an operant behavior during non-reinforcement. This effect is consistent with Kurylo and Tanguay [21], and the higher dose used here produced an even greater effect than 0.30 mg/kg used previously. In this regard, treated animals did not alter the conditioned behavioral pattern in response to withholding reward, again indicating reduced sensitivity to this change in condition.

QNP had a differential effect on early and late components of the behavioral sequence, reflected by differences in the operant and consummatory behaviors (Fig. 2B and D, respectively). Non-reinforcement produced perseveration of the operant–consummatory response sequence. In contrast, perseveration of the consummatory behavior, reflected by time in the drinking well, occurred in the presence of reward, but not during non-reinforcement. This differential effect of QNP may be related to the position of the behavior in the sequence. The operant behavior (nose-poke followed by entry into the drinking well), which is more distal to the acquisition of reward, is maintain during non-reinforcement, whereas perseveration of the consummatory behavior (du-

ration within the drinking well), which is more proximal to the reward, is linked to the presence of water.

The behavior of the 0.08 mg/kg dose group paralleled that of control subjects, with the exception of reduced acquisition. The acquisition effect with the 0.08 mg/kg dose group may reflect selective activation of dopamine autoreceptors [13,49,50], thereby reducing dopamine activity. However, once the operant behavior was learned, performance was normal. In this regard, following acquisition, animals in the low dosage group did not appear sedated, but instead performed at a level of activity consistent with the control group.

Results described here, combined with reported effects on spontaneous behaviors [8,17,35,44] and reduced behavioral variability [6,9,10,44], supports the hypothesis that QNP reduces the capacity to adjust operant behaviors in order to maintain effective interactions with the environment. This effect is consistent with QNP interfering with signals associated with omission of a predicted reinforcer. Nucleus accumbens dopamine levels increase during operant responses [19,24,32,42], which is not associated with food consumption [32] or reinforcement magnitude [42]. Reduction or omission of predicted reinforcers is associated with a phasic decrease in tonic dopamine activity [39]. Such a signal may serve to initiate behavioral changes to accommodate changing conditions. By interfering with this signal, QNP reduces adaptability to changing contingencies, maintaining behaviors in the absence of reinforcement.

Analysis of neural mechanisms associated with perseveration effects of QNP would facilitate developing neurochemical models for psychiatric conditions that include perpetuated behaviors that are ineffective or inappropriate, such as obsessive-compulsive disorder [45,46] or maladaptive repetitive behaviors observed with schizophrenia [29,52].

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