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Effects of quinpirole on behavioral extinction

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Abstract

Behavioral effects of quinpirole (QNP), a dopamine D_2 receptor agonist, suggest it impacts neural mechanisms mediating goal-directed behaviors, as well as behavioral extinction following removal of a primary reinforcer. The present study investigated the effect of QNP on behavioral extinction following the omission of contingent reinforcement, and whether this effect is related to acquisition or processes specific to extinction. Rats were trained on a continuous reinforcement schedule to nose-poke for water reward. Using a free-operant procedure, rats completed approximately 70 responses for each of four consecutive days. On the fifth day reward was withheld. Rats were assigned to one of five groups in which they received 0.3 mg/kg QNP ip either during the first day (acquisition phase), the second 2 days (maintenance phase), the last day (extinction phase), or during all days. A fifth group received vehicle injections. Rats receiving QNP during the acquisition and maintenance phase did not differ significantly from the control group during the extinction phase, although they demonstrated reduced response rates on days they received QNP. However, rats treated during the extinction phase or during all phases demonstrated a significant reduction in the rate of extinction. This effect cannot be attributed to an increase in general behavioral arousal because response rates for reinforced responses did not differ significantly among groups following acquisition of the behavior. The reduced extinction effect does not appear to be related to abnormalities in the initial behavior–reward association, but instead may result from enhanced engagement of learned behavioral patterns, or from interference of signals associated with removal of predicted reinforcement.

Keywords: Quinpirole; Dopamine; D_2 receptors; Extinction; Reinforcement; Schizophrenia; Obsessive–compulsive disorder

1. Introduction

Dopaminergic systems play an important role in selecting behavioral responses, as well as mechanisms mediating conditioned reward. Such processes guide the establishment of goal-directed behaviors. The impact of dopamine systems on behavioral responses may be explored by examining effects on operant conditioning [1,2]. In addition to studies on the reinforcing properties of neurochemicals using secondary (conditioned) reinforcement, dopamine's role in the acquisition, maintenance, and extinction of operant responses established by primary reinforcement has been examined. Reduced dopamine activity disrupts acquisition of operant responses [3–5]. In addition, selective dopamine receptor antagonists reduce operant responding for primary reinforcement from food [6–9], water [10–13], or electrical stimulation [14]. Dopamine depletion by means of 6-OHDA applied to the nucleus accumbens [9,15], as well as to the medial striatum or ventrolateral neostriatum [9], also reduces operant responding.

With regard to extinction, dopaminergic systems play a role in response reduction that results from removal of primary reinforcement. Response reduction produced by dopamine receptor antagonists resembles extinction produced by nonreinforcement [16,17], although differences in response patterns exist [18–21]. A finer analysis of the response reduction produced by dopamine depletion indicates that compared to controls, treated rats show less within-session response decline, and greater interresponse pause length [9,21,22]. Results from extinction studies suggest that dopamine receptor antagonists affect incentive-related motor activity [23]. Furthermore, considerable evidence indicates that interference with dopamine transmission does not block primary food reinforcement [3,7,9,18,21–25].

Nucleus accumbens dopamine levels increase during operant responses [24,26–28], which is not associated with

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food consumption [26] or reinforcement magnitude [28]. Reduction or omission of predicted reinforcers is associated with a phasic decrease in tonic dopamine activity [29]. This effect is consistent with response patterns produced by dopamine depletion during intermittent reinforcement schedules. Administration of a dopamine D_2 receptor antagonist (pimozide) during the nonreinforced component of an intermittent reinforcement schedule produced a greater response reduction than nonreinforcement alone [16,17]. Furthermore, nucleus accumbens dopamine depletion interfered with reinforcement schedules that required higher rates of responding, but not those that required moderate rates [22,25]. These results suggest that nucleus accumbens dopamine is involved with behaviors that require higher response rates to elicit reinforcement [22] as well as the maintenance of behaviors during periods of nonreinforcement [16,25].

Lacking from this research is an examination of the effects of dopamine agonists during extinction in which the primary reinforcer is withheld. Based upon neurochemical and behavioral effects of nonreinforcement, it is hypothesized that administration of a D_2 agonist during the period of nonreinforcement would reduce behavioral extinction by interfering with signals of the omission of predictive reward. The established operant responses would thereby continue in the absence of reinforcement.

Quinpirole (QNP), a dopamine D_2 family agonist, was used to examine effects of D_2 activation during nonreinforcement. QNP has been associated with perseveration and stereotypy, which are related to abnormalities in selecting behavioral responses. Chronic systemic administration of QNP produces behavioral sensitization, characterized by hyperlocomotion and stereotypy [30–32]. These effects were observed in open field or test chambers in animals receiving ad lib water and food. Systemic administration of QNP also produces stereotypy, including repetitive oral behaviors, such as mouthing, sniffing, and licking [33–36]. Chronic QNP treatment also causes reduced behavioral variability, which is characteristic of perseveration. QNP treatment also caused repeated travel along routes confined to a limited area [37,38]. To examine whether decreased behavioral variability was a secondary effect of increased nonspecific behavior, Eilam et al. [38] measured spontaneous alteration behavior. Food-deprived rats navigated a T-maze to locate a food reward. Chronic QNP treatment reduced spontaneous alteration behavior that was not attributable to motor hyperactivity. QNP's behavioral effects thereby appear to be increased locomotor activity with an abnormality in the selection of specific behavioral patterns.

To examine QNP's impact on established behavioral patterns, measurements were made of changes of operant responses following the removal of contingent reinforcement. To examine which components of operant conditioning are affected by QNP, acute treatment was given either during the acquisition, maintenance, or extinction phase of conditioning. A further group received QNP during all phases of conditioning.

2. Experimental procedures

2.1. Subjects

Fifty Long–Evans rats (Charles River Breeding Laboratory), at 60 to 120 days of age, served as subjects. Animals were housed in a temperature-controlled facility that was maintained on a 12-h light/dark cycle. This study was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was approved by the Institutional Animal Care and Use Committee of Brooklyn College.

2.2. Apparatus

Behavioral measurements were made in an operant conditioning chamber that contained a front panel on which an opening led to a glass funnel. The outer section of the funnel was positioned between an infrared (I/R) emitter–detector pair. Head placement within the funnel interrupted the I/R beam, which was detected by computer. Six centimeters to the left of the funnel opening was a recess that contained a drinking spout from which a measured amount of water (approximately 0.04 ml) could be delivered by means of a solenoid driven valve. Circuitry for the I/R pair and the solenoid was interfaced via solid-state relay switches to a computer. Session events and data collection are controlled by computer.

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 lib in their home cages for 1 h after each session. Sessions were held once per day for six 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. Acquisition phase

Following magazine training, rats were conditioned with a free-operant procedure with continuous reinforcement to place their heads within the funnel in order to receive a single delivery of water from the drinking spout. Training was considered complete when rats completed 75 responses, which was reached within a single session. The time at

which each response occurred was recorded throughout the session.

2.3.3. Maintenance phase

In order to establish reliable behavior as well as a gradual decline in response rate during the extinction phase, rats underwent three sessions of maintenance conditioning. During these sessions, rats received reward each time they placed their head into the funnel, for a total of 70 responses (± 5) per session. In this regard, all animals completed the same number of responses during the acquisition and maintenance phases. Maintenance phase sessions were typically completed in approximately 7 min.

2.3.4. Extinction phase

On the day following the third maintenance session, rats were placed into the chamber, but reward delivery was withheld. Responses continued to be tracked throughout the session. On this final day of testing, rats remained in the chamber for at least 90 min. Animals who continued to respond remained in the chamber beyond this time until responses ceased for approximately 10 min.

2.4. Treatment groups

Rats were randomly assigned to one of five treatment groups (10 rats per group) (Fig. 1) in which they received either QNP hydrochloride (Sigma-Aldrich) (0.3 mg/kg, dissolved in saline) or sterile saline, delivered intraperitoneally 1 h before sessions. An equal number of male and female rats were assigned to each group. The acquisition group received QNP during the acquisition phase, and receive saline during all other phases. The maintenance group received QNP during the first 2 days of the maintenance phase (QNP was not administered on the third day of the maintenance phase in order to reduce possible residual effects during the extinction phase after successive days of administration), and saline during all other phases. The extinction group received QNP during the extinction phase, and saline during all other phases. The all-phases group received QNP during all phases. The fifth group served as the control group, in which rats received saline during all phases of the experiment.

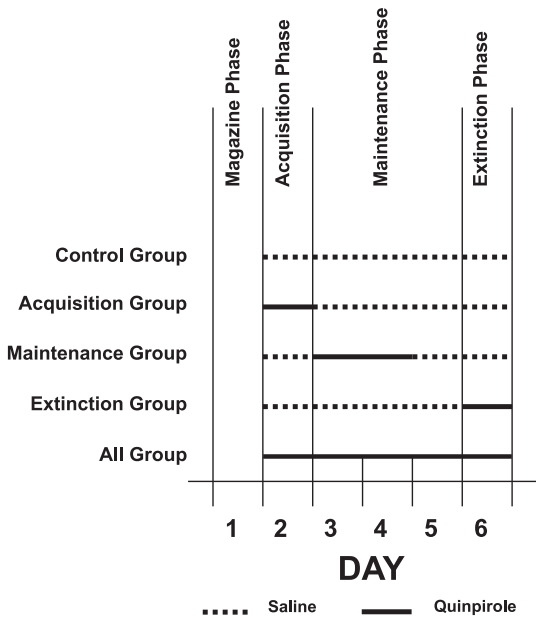

Fig. 1. Conditioning sequence and drug treatment schedule. Five groups of rats received either quinpirole or saline at different phases of operant conditioning.

3. Results

Response rates (mean number of responses per minute) for all sessions, and number of responses during the extinction phase, were compared among subject groups. A response sequence included the operant and consummatory phases.

3.1. Rate of responding

Response rates were compared among subject groups for the first four sessions (acquisition phase and maintenance phase) (Fig. 2), in which water was delivered after each response. An analysis of variance (ANOVA) indicated a main effect of subject group [$F(4,45)=2.81$, $P<.05$], a main effect of day [$F(3,135)=101.99$, $P<.01$], and an interaction of group by day [$F(12,135)=3.56$, $P<.01$]. To interpret the interaction, post hoc Dunnett's tests were performed to compare treatment groups to the control group for each day. On Day 1, the acquisition group and all-phases group (both of which were treated with QNP) responded at significantly lower rates than the control group ($P<.05$), whereas the maintenance and extinction groups (which did not receive treatment on Day 1) did not. On Day 2, the maintenance group and all-phases group (both of which received QNP) responded at significantly lower rates than the control group, whereas the acquisition and extinction groups (which did not receive QNP on Day 2) did not. On Days 3 and 4, no significant differences in rate were found between the control group and other groups. Slower response rates for treated groups seen in early training sessions and not in subsequent sessions suggest that QNP interfered with responding during the acquisition of the task, but once the task was learned, response rates were comparable to control animals.

3.2. Extinction

The criterion for behavioral extinction was defined as a lack of responding for at least six consecutive minutes. Number of responses to extinction for each subject group is depicted in Fig. 3. One rat from the all-phases group responded at more than 3 standard deviations above other rats in that group (797 responses before finally extinguish-

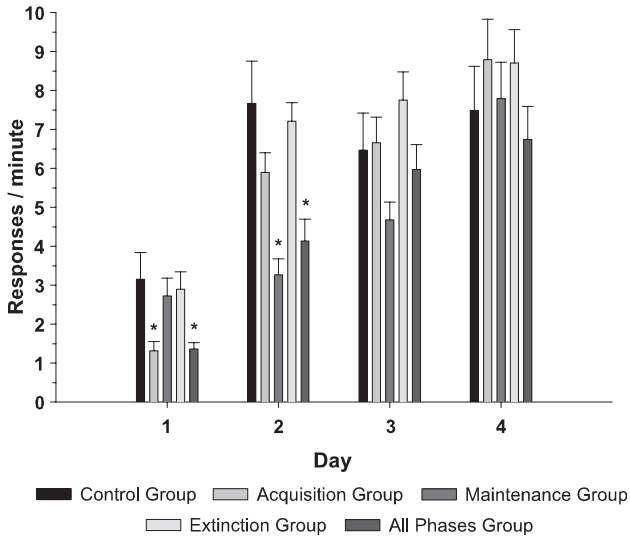

Fig. 2. Mean and S.E.M. of response rate for each subject group across each day in which reward was delivered. Asterisks indicate significant differences ($P < .05$) from the control group.

ing its behavior after 2 h and 29 min), and was therefore not included in the analysis or figures. For responses to extinction, ANOVA indicated a significant effect of subject group [$F(4,39) = 3.59$, $P < .05$]. Post hoc Dunnett's test indicated that the extinction group and the all-phases group differed significantly from the control group ($P < .05$), whereas the acquisition and maintenance groups did not.

In order to gain a finer analysis of the extinction process, response rates were tracked for each 4-min interval throughout the extinction phase (Fig. 4). For the control group, the extinction phase began with a mean response rate of 49% of the previous day, then sharply diminished over the first 16 min, then diminishing more gradually until extinguishing at a mean of approximately 62 min. Following a period of no or minimal responses, a slight renewal in responding occurred near the end of the session.

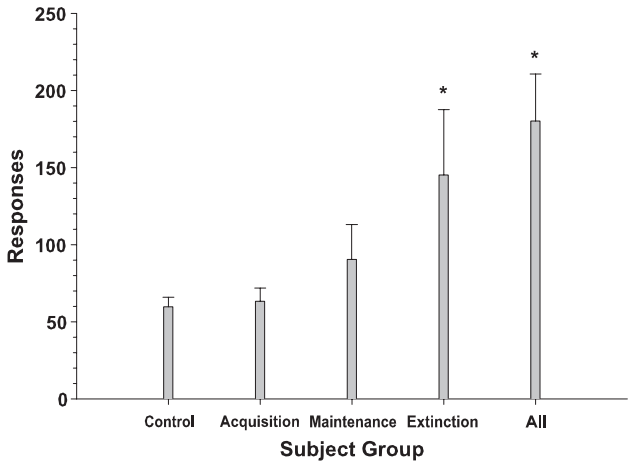

Fig. 3. Mean and S.E.M. responses to extinction for each subject group. Asterisks indicate significant differences from the control group.

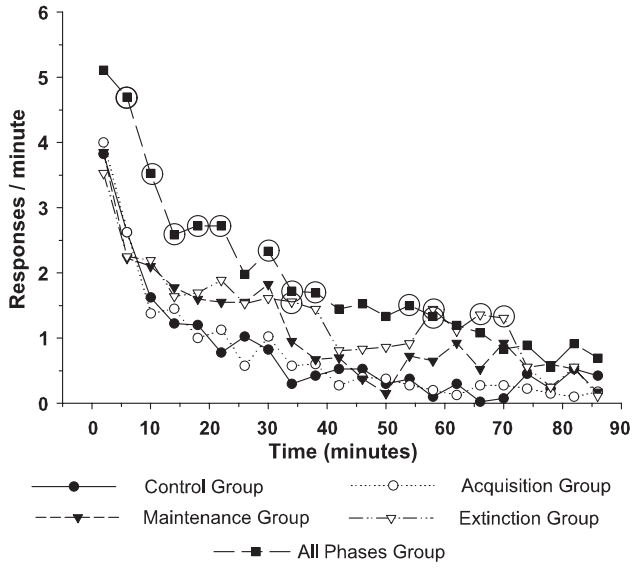

Fig. 4. Mean response rate for each subject group as a function of time (in 4-min intervals) during the extinction phase. Circled symbols indicate significant differences from the control group.

A two-way (Subject group × Time) ANOVA, with repeated measures on the time factor, indicated a main effect of time [$F(21,924) = 45.19$, $P < .01$], and a Group × Time interaction [$F(84,924) = 1.34$, $P < .05$]. Dunnett's tests indicated that the acquisition group and the maintenance group did not differ significantly from the control group at any time interval. However, the extinction group differed from the control group at the 34-, 58-, 66-, and 70-min intervals, and the all-phases group differed from the control group at the 6–22, 30–38, 54, and 58-min intervals.

4. Discussion

The principal result is that QNP reduced extinction of operant responses when primary reinforcement was withheld. This effect was not due to generalized behavioral arousal, since subject groups did not differ significantly in response rate on the 2 days prior to the extinction session. The only differences found in response rate during water reinforcement was on the first 2 days of operant conditioning, in which treated groups responded at lower rates than untreated groups. Accounts of the reduced extinction effect must include a mechanism that maintains the conditioned behavior in the absence of external reward. Because reduced extinction did not occur in animals that received QNP only during the acquisition or maintenance phase of conditioning, it appears that the manner in which the behavior is first established does not later impact extinction. This result is thereby inconsistent with models in which QNP modifies the emergence of behavior–reward associations, for example, by diverting the association to an internal reinforcement source, or by amplifying behavior–reward pairing.

Reduced extinction did occur in animals treated only during the extinction phase, suggesting that the effect of QNP is specific to processes active during extinction. This result may be modeled as either the disruption of processes altering behavior during extinction, or a shift in behavioral control from an external to an internal source of reinforcement. Predominant theories of extinction address behavioral changes resulting from changes to reinforcement contingencies present during acquisition, either through response inhibition, interference by a new set of responses, or progressive change in the predicted effects of behavior. Each of these processes may play at least a partial role in extinction [39].

Inhibitory effects result from learning that the expected reinforcer is no longer contingent upon the behavior, thereby suppressing the response. QNP may slow inhibition by interfering with the new learning. Such an effect is consistent with results from the acquisition phase of conditioning, in which treated animals were slower to learn the operant response. In this regard, changes to reinforcement contingencies during the extinction phase represent new conditions that need to be learned for extinction to occur. Interference to learning by QNP may thereby disrupt acquisition of new behaviors. In this context, reduced extinction represents reduced ability to acquire new behaviors with changing conditions.

For interference theories, new responses that result from omission of the expected reward are temporarily elicited at the beginning of extinction. Interfering responses may be generated by frustration, invoking emotional processes [40]. Effects of QNP on limbic dopaminergic systems could impact such processes, thereby reducing interference of the original behavior.

For theories based upon changes in the predicted effect of behaviors, the outcome of previous responses are used to predict that of future responses. During extinction, responses with no reward progressively replace the memory of rewarded responses [41]. Effects of QNP on reinforcement mechanisms could act to lessen the impact of nonrewarded responses, thereby maintaining behaviors established by the original reinforcement contingencies.

The most profound extinction effect occurred with animals treated throughout conditioning. This result may reflect a cumulative effect of repeated QNP administration. Hyperlocomotion has been reported for rats receiving 10 or more injections over a period of several days [30,42]. In addition, QNP produced a period of behavioral inhibition during the initial phase of administration [43,44]. Biphasic and cumulative action of QNP could therefore concealed possible action of QNP in rats treated only during the acquisition and maintenance phases, and best produce the effect when administered during all phases.

Neural mechanisms underlying QNP's extinction effect are uncertain. The mesolimbic dopaminergic system originating in the ventral tegmental area and projecting to forebrain regions, including nucleus accumbens, is associated with mediating reward-related behaviors (e.g. Ref. [45]). Nucleus accumbens dopamine may be involved in maintaining behaviors during periods of nonreinforcement [25]. Decreased activation of dopamine neurons in multiple areas is associated with omission of a predicted reinforcer [29]. QNP may reduce behavioral extinction by interfering with these signals, thereby maintaining established behaviors regardless of changes in reinforcement contingencies.

The nigrostriatal dopaminergic system arising from substantial nigra and projecting to the caudate nucleus and the putamen appear to mediate motor components of operant responses [46,47]. Activation of this system by QNP may excessively engage established behavioral patterns, thereby interfering with the acquisition of new patterns as well as maintaining behavior in absence of external reward.

Operant behaviors during the extinction phase may also be maintained by contextual cues that have acquired conditioned reinforcing properties. During conditioning, environmental cues associated with the testing area become associated with the primary reinforcer and thereby derive control over behavior. Behavioral responses to conditioned reinforcers have been associated with increased activation of nucleus accumbens dopamine receptors [48–50]. In this regard, QNP may enhance behavioral control by conditioned reinforcers, maintaining operant responses in the absence of water reinforcement.

Reduced extinction by QNP may reflect a more general effect of perseveration. Reduction in behavioral variability would decrease exploration, thereby interfering with learning. This prediction is consistent with slower response rates during acquisition for treated groups found here, as well as with reduced spontaneous alteration found with T-maze exploration [51]. Similarly, microinjection of QNP into nucleus accumbens reduced or moderated exploratory locomotor activity [52,53]. Perseverance of behavioral patterns could also result in resistance to modify learned behaviors in response to changes to reinforcement contingencies.

Behavioral effects of QNP may model behaviors associated with obsessive–compulsive disorder [43,54]. Similarly, effects of QNP may parallel behaviors found in schizophrenia [55], which is associated with heightened D_2 activity in the mesolimbic dopaminergic system [56,57]. In each case, disruption of dopamine mechanisms produces abnormal internal reinforcement function, which leads to perpetuated behaviors that are ineffective or inappropriate.

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