Pharmacology Biochemistry & Behavior, Vol. 25, pp. 1191–1194, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

The Schedule Dependent Effects of 3-Quinuclidinyl Benzilate on Operant Behavior in the Rat

WU-FU LIU

Laboratory of Behavioral Pharmacology and Toxicology
CSIST, P.O. Box 1-4-9, Lung-Tan, Taiwan, Republic of China

AND

JOHN M. BEATON[1]

Neurosciences Program and Department of Psychiatry
University of Alabama at Birmingham, Birmingham, AL 35294

Received 17 December 1985

LIU, W.-F. AND J. M. BEATON. *The schedule dependent effects of 3-quinuclidinyl benzilate on operant behavior in the rat.* PHARMACOL BIOCHEM BEHAV **25**(6) 1191–1194, 1986.—The effects of 3-quinuclidinyl benzilate (QNB) on performance maintained by a fixed-ratio 20 (FR-20) or a differential-reinforcement-of-low-rate 20 sec. (DRL-20) schedule for water reinforcement were studied in rats. Graded doses of QNB (range 0.0125–0.2 mg/kg) were administered IP immediately prior to 30 min test sessions. QNB had a biphasic effect on FR responding: at a low dose (0.0125 mg/kg) it increased, while at higher doses (0.05–0.2 mg/kg) it decreased mean response rate in a linear, dose-dependent, manner. QNB had only a monotonic effect on DRL responding; doses of 0.05–0.2 mg/kg increased the mean response rate and decreased reinforcement rate in a dose-related fashion. The ED_{50}'s for loss of reinforcement were identical (0.07 mg/kg) for both schedules. The findings indicate that QNB may exert rate dependent effects.

Rate dependency QNB FR performance DRL performance

THE effects of central muscarinic antagonists, such as atropine, scopolamine or benactyzine, on schedule-controlled behavior have been extensively studied. A response-rate-dependent monotonic effect on the overall rates of responding maintained by schedules such as the fixed-ratio (FR), fixed interval (FI) or differential-reinforcement-of-low-rate (DRL) has frequently been observed following the systemic injection of anticholinergics. In general, central anticholinergic drugs induce a decrease in the high rate of responding generated by FR schedules [10], but an increase in the low rate of responding generated by DRL schedules for rat studies [3, 5, 8, 9].

In order to evaluate the finding of an inverse relationship between the control rate of responding and the effects of the anticholinergic drug on response rates, a general technique used involves the comparisons of drug effects on rates of responding maintained by several different schedules of reinforcements. The present experiment was undertaken to assess the effects of QNB on bar-pressing behavior maintained by two schedules of water reinforcement which induce differential baseline rates of responding, namely the high response rate generated by the FR-20 schedule and the low response rate generated by the DRL-20 sec. This was carried out to allow us to evaluate whether or not QNB induces the same response-rate-dependent effects observed with traditional anticholinergic drugs.

METHOD

Sixteen experimentally naive male Sprague-Dawley rats (bred in Taiwan) were used. Eight rats were randomly assigned to each experiment (FR and DRL). The rats weighed 200–250 g at the start of the experiment. All animals were maintained on a 23½ hr per day water deprivation schedule. Food was freely available in the home cages which were located in a room in which the temperature was maintained at approximately 20°C. The lights were on from 7 a.m. to 8 p.m.

Apparatus

The experiments were conducted in two identical

[1]Requests for reprints should be addressed to Dr. John M. Beaton, Neurosciences Program, University of Alabama at Birmingham, Box 190, University Station, Birmingham, AL 35294.

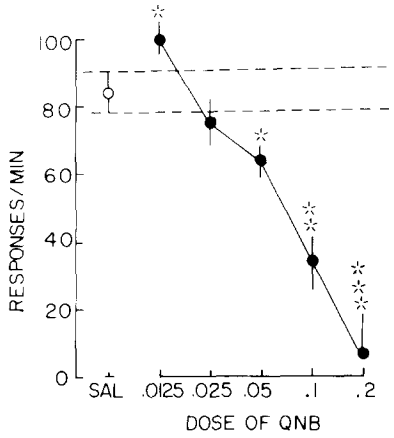

Fig. 1. The effect of QNB on response rate for an FR-20 schedule of water reinforcement. Each value represents the mean±SEM of eight readings. $*p<0.05$, $**p<0.01$, $***p<0.001$, comparison with saline control by the Dunnett t-test following the detection of an overall significance ($p<0.001$) with an ANOVA test.

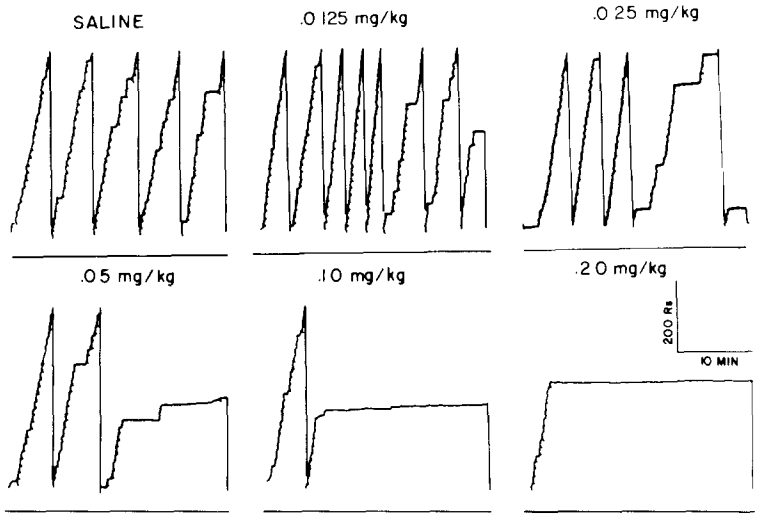

FIG. 2. Cumulative response records showing the effects of gradual doses of QNB on responding of a rat by an FR-20 schedule of water reinforcement.

BRS/LVE operant chambers. Each was equipped with a dipper which delivered 0.05 ml of tap water, and a single lever which required a force of 10–15 g to operate. Programming and data recording were performed with electromechanical circuits, counters and cumulative recorders.

Procedure

FR. The general procedure and the experimental design have been described previously [6]. Briefly, the rats were first trained to lever press on a continuous reinforcement (CRF) schedule for water reinforcement. Daily sessions were 30 minutes in duration. Each animal was tested at the same time each day, five days a week; running order of subjects was constant. After all rats were responding consistently on the CRF schedule (approximately 3–5 days), an FR schedule was introduced and gradually increased to an FR-20. After the response rate for all rats had stabilized, drug testing was begun. There was no significant drift in the response rate on saline sessions during the experiment.

DRL. The animals were first trained to lever press on a CRF schedule for water reinforcement. Daily sessions were of 30 minutes duration. Each animal was tested at the same time of day, five days a week; running order of the rats was constant. After the rats were responding consistently on the CRF schedule (approximately 3–5 days) a DRL schedule was introduced and gradually (2–4 weeks) increased to DRL-20 sec. With this schedule only lever presses, which followed a delay of 20 sec or more after the previous response, were reinforced. After an additional 2–3 weeks of control DRL-20 sessions, during which the rate for all rats stabilized, drug testing was begun. The baseline rates on saline days did not change significantly over time.

Drug testing. QNB HCl was synthesized and donated by J. S. Ho from the Department of Chemistry, CSIST (Taiwan, R.O.C.). It was dissolved in a sterile saline solution and

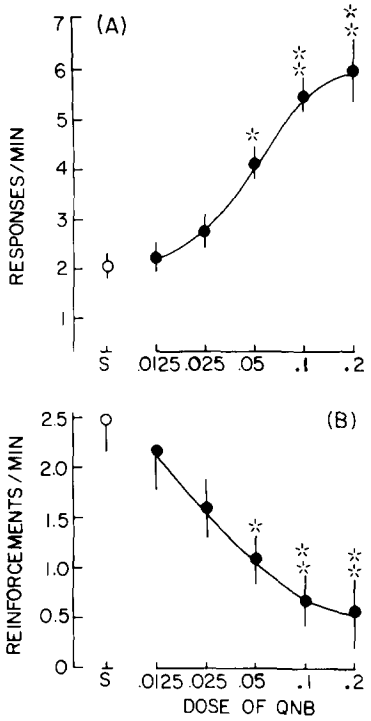

FIG. 3. The effects of QNB on response rate (Panel A) and reinforcement rate (Panel B) for a DRL-20 sec schedule of water reinforcement. Each value represents the mean±SEM of eight readings, $*p<0.01$, $**p<0.001$, comparison with saline control by the Dunnett t-test followed by a significant overall drug-related effect ($p<0.001$) with an ANOVA test.

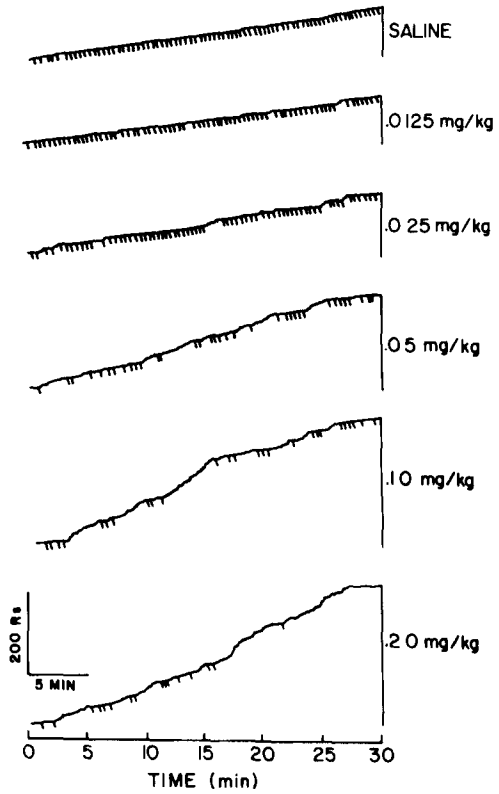

FIG. 4. Cumulative response records showing the effects of graded doses of QNB on responding of a rat by a DRL-20 sec schedule of water reinforcement.

injected IP in volumes=2.0 ml/kg. During drug testing on Fridays, each rat received an IP injection of either 2.0 ml/kg isotonic saline or 0.0125, 0.025, 0.05, 0.1, and 0.2 mg/kg QNB HCl. Drug sessions were preceded by two consecutive saline nondrug control sessions (Wednesday and Thursday). There were no significant differences in performance on these days and the data for the Thursday session were designated as the saline control data. All drug or saline injections were administered immediately prior to testing. The order of the doses administered was randomized for each rat.

Statistical analysis. For both studies, the response rate for the control and drug conditions were calculated as mean responses per min. The dose-response relationship was examined by using a one-way analysis of variance (ANOVA) with repeated measures, in a block design, followed by Dunnett's t-test (two-tailed), where $p<0.05$ was considered as an overall significant drug effect. ED_{50} values for behavioral disruption, estimated from the statistically significant decrement in percent of response of reinforcement rate for QNB compared to saline control as shown from data illustrated in Figs. 1 and 3, were determined using probit analysis [7].

RESULTS

FR-20

The average control FR 20 response rates (±SEM)=84±6 responses per min during saline treatment. Control performance was characterized by a rapid, constant rate of responding throughout the session. The effects of QNB on the average response rate are shown in Fig. 1. Evaluation of data from the saline control session and the doses of QNB treatments using a one-way ANOVA with repeated measures yielded a significant overall drug effect, $F(5,35)=7.5$, $p<0.001$. Response rate was increased with the low dose (0.0125 mg/kg) and decreased dose-dependently with moderate to high doses (0.05–0.2 mg/kg). No significant effects were found at 0.025 mg/kg because of the high degree of intersubject variability.

Cumulative records illustrating the effects of saline and various doses of QNB on FR-20 responding of one rat are depicted in Fig. 2. The 0.0125 mg/kg dose of QNB produced an apparent increase in responding which began approximately 5 min after the injection and lasted approximately 8 min. QNB doses of 0.025 to 0.2 mg/kg produced a dose-related suppression on FR responding, which was characterized by extended pausing or complete cessation of responding.

DRL-20

The average control DRL-20 response rates and reinforcement rates (±SEM) were 2.1±0.1 and 2.5±0.2 counts per min respectively. QNB exerted significant overall effects, $F(5,35)=6.8$, $p<0.001$; $F(5,35)=6.4$, $p<0.001$, on both measures of DRL performance (Fig. 3). A dose-dependent increment in mean response rate and a concomitant decrease in mean reinforcement rate were observed, with significant effects, at doses of 0.05 up to 0.2 mg/kg when compared to the average control performance.

Cumulative records illustrating the effects of saline and the doses of QNB on DRL-20 responding of one rat are shown in Fig. 4. The saline control session was characterized

by a slow, constant rate of responding, with regular reinforcement delivery. At doses of 0.05, 0.1 and 0.2 mg/kg QNB there were significant increases in short latency nonreinforced responding accompanied by loss of regular reinforcement delivery.

With respect to the efficiency of the behavioral disruption, the median effective doses (ED_{50}'s) with 95% confidence limits [7] estimated from the decrement in percent reinforcement rate for QNB compared to the saline control, were 0.07 (0.04–0.11) and 0.07 (0.04–0.14) mg/kg for the FR-20 and DRL-20 performances, respectively.

DISCUSSION

The major findings of the present study on the QNB dose effect determinations were that the high rate of responding generated by the FR-20 schedule decreased, and the low rate of responding generated by the DRL-20 schedule increased at the same doses, ranging from 0.05 to 0.2 mg/kg. These results following the QNB injections can be interpreted in terms of the rate dependency hypothesis [1,4]. This hypothesis states that there is an inverse relationship between the schedule control rate of responding and the rate of responding in the drug conditions. These data are in accordance with the results from previous studies in the rat with other anticholinergics [3, 5, 8–10]. The only exception was with 0.0125 mg/kg QNB where the rate of responding on FR-20 was increased but there was no opposite effect (i.e., a decrement) in DRL-20 performance.

In the DRL experiment, although no interresponse time (IRT) data were recorded, the cumulative records (Fig. 4) show clearly that (1) a stable temporal discrimination had been established under control conditions, (2) much less pausing or complete cessation of responding was observed during the QNB sessions than with the FR performance, and (3) the temporal discrimination was disrupted as indicated by a dose-related decrease in efficient responding performance.

The identical ED_{50}'s suggest that the above schedules are equally sensitive to the disruptive effects of QNB. The present experiments, through manipulating response rates by using different schedules (FR and DRL), have shown the same response-rate-dependent effects as with amphetamine [2].

In conclusion, QNB appears to exert schedule induced response-rate-dependent effects with moderate to higher dose levels (0.05–0.2 mg/kg) and induces identical decrements of behavioral disruption on FR and DRL performances (ED_{50}'s=0.07 mg/kg).

REFERENCES

1. Dews, P. B. Studies on behavior, IV. Stimulant actions of methamphetamine. *J Pharmacol Exp Ther* **122:** 137–147, 1958.
2. Dews, P. B. Analysis of the effects of pharmacological agents in behavioral terms. *Fed Proc* **17:** 1024–1030, 1958.
3. Ellen, P., W. C. Aitken, T. Sims and J. M. Stahl. Cholinergic blockade, septal lesions, and DRL performance in the rat. *J Comp Physiol Psychol* **89:** 409–420, 1975.
4. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of behavioral effects of drugs. *Ergeb Physiol* **60:** 1–56, 1968.
5. Kelsey, J. E. and S. P. Grossman. Influence of central cholinergic pathways on free operant avoidance and DRL schedules. *Pharmacol Biochem Behav* **3:** 1043–1050, 1975.
6. Liu, W. F., N. W. Hu, T. F. Chien and J. M. Beaton. Effects of 3-quinuclidinyl benzilate on fixed-ratio responding and open-field behavior in the rat. *Psychopharmacology (Berlin)* **80:** 10–13, 1983.
7. Litchfield, J. T. and F. S. Wilcoxon. A simplified method of evaluating dose-affect experiments. *J Pharmacol Exp Ther* **96:** 99–113, 1949.
8. McGuire, P. S. and L. S. Seiden. The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rates schedule in rats. *J Pharmacol Exp Ther* **214:** 635–641, 1983.
9. Meyer, M. E., G. A. Severson and R. W. Thompson. Scopolamine, methylscopolamine, and response conditional inhibition in the rat. *Physiol Psychol* **4:** 43–44, 1976.
10. Pradhan, S. N. and T. Roth. Comparative behavioral effects of several anticholinergic agents in rats. *Psychopharmacologia* **12:** 358–366, 1968.