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Differential effects of carbamazepine on negatively versus positively reinforced responding

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Abstract

To assess its effects on negatively versus positively reinforced operant behavior, carbamazepine (CBZ) or vehicle was acutely administered to rats. Negative reinforcement baselines consisted of a free-operant avoidance task with 5-s shock–shock and 20-s response–shock intervals. Positive reinforcement baselines consisted of responding for food pellets on a variable interval 30-s schedule. Ascending dose–effect functions were established using CBZ for negatively reinforced responding (vehicle, 25, 50, 100 mg/kg ip) and positively reinforced responding (vehicle, 12.5, 25, 50, 100 mg/kg ip). Negatively reinforced responses and avoided shocks were significantly reduced by CBZ injections at 100 mg/kg. Positively reinforced responses and food pellet deliveries were significantly reduced by CBZ injections at 25, 50, and 100 mg/kg. The results show that CBZ has differential, dose-dependent effects on negatively versus positively reinforced responding.

Keywords: Carbamazepine; Antiepileptic; Operant behavior; Negative reinforcement; Free-operant avoidance; Positive reinforcement; Variable interval schedule; Rat

1. Introduction

Carbamazepine (CBZ) is an iminostilbene derivative commonly used as an antiepileptic drug (AED) to treat simple and complex partial seizures, and generalized tonic–clonic seizures (Kubova and Mares, 1993). Similar in structure to the tricyclic antidepressant imipramine, CBZ is used alone or in combination with lithium carbonate for manic–depressive illness and is the drug of choice for treatment of trigeminal neuralgia (Macdonald, 1995). Although its mechanisms of action have not been completely identified, CBZ appears to have widespread effects within the CNS, the most important of which is the stabilization of voltage-dependent sodium channels. CBZ preferentially binds to sodium channels that are in the inactive state and produces a time-dependent, use-dependent, and voltage-dependent block of sodium channels that results in the slowing of sodium channel recovery from inactivation (Macdonald and Kelly, 1995; Macdonald and Meldrum, 1995; Schwarz and Grigat, 1989). In addition, CBZ influences a variety of neurotransmitter systems, including adenosine (Marangos et al., 1983, 1985; Skerritt et al., 1983), somatostatin (Rubinow et al., 1984), dopamine (Post et al., 1986; Barros et al., 1986), peripheral benzodiazepine receptors (Weiss et al., 1985), GABA receptors (Foong and Satoh, 1984), acetylcholine (Consolo et al., 1976), and substance P (Post, 1988).

Although the effects of CBZ on cellular and molecular targets have received considerable research attention, less is known about its effects on operant behavior. This is a clinical concern because the use of AEDs has been associated with negative side effects, particularly sedation (Alvarez et al., 1998; Collaborative Group for the Study of Epilepsy, 1986). Although AEDs such as CBZ may have positive effects on seizure activity, they may also produce cognitive and behavioral impairments that have yet to be

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identified. Behavioral psychopharmacology studies of CBZ have shown reductions in avoidance acquisition, suggesting that the drug may impair the acquisition of negatively reinforced behavior (Banks et al., 2001; Voigt and Morgenstern, 1992). Conversely, a study by Evenden and Ryan (1996) has shown that CBZ does not effect delayed choice responding maintained on schedules of appetitive reinforcement. These studies suggest a differential pattern of effect for CBZ on negatively versus positive reinforced responding. However, the negative reinforcement analyses studied acquisition and the positive reinforcement analysis studied steady-state behavior. Therefore, it is unclear whether the qualitatively different effect of CBZ on operant behavior is a function of reinforcer type or performance acquisition.

To help clarify the behavioral effects of CBZ, we established steady-state baselines for negative reinforcement in the form of free-operant avoidance and positive reinforcement in the form of variable interval (VI) appetitive reinforcement. Dose–effect functions were then established for both types of reinforcers to assess the effects of CBZ on responding. By conducting this analysis, we sought to identify whether CBZ has differential effects on negatively versus positively reinforced steady-state, operant behavior.

2. Materials and methods

2.1. Subjects

Sprague–Dawley male rats, obtained from Harlan, served as subjects. Animals were individually housed with ad libitum access to water. At the start of the experiment, animals were approximately 100 days old and weighed approximately 400 g. For animals exposed to the appetitive reinforcement schedule, food intake was restricted throughout the experiment so that the animals' weights were maintained between 400 and 425 g (feeding occurred approximately 1 h after completion of the daily session). No food restriction occurred for animals in the negative reinforcement analysis. During the experiment, a 12:12 light/dark cycle (with lights on at 6:00 a.m.) was in effect; experimental sessions occurred during the lights-on cycle.

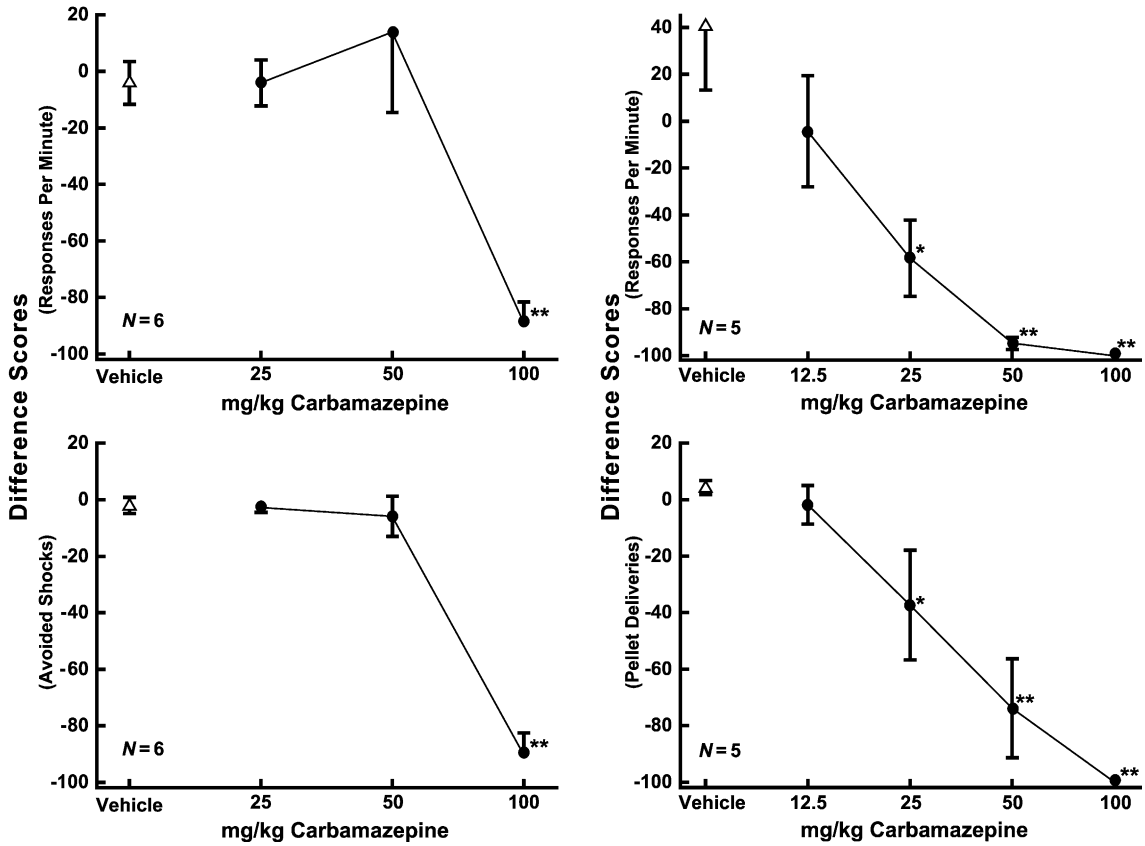

Fig. 1. The effect of different doses of CBZ (vehicle, 25, 50, and 100 mg/kg) on behavior. The left-hand panels display the effects of CBZ on negatively reinforced responding ($n = 6$). The task was a free-operant procedure with a 5-s shock–shock interval and a 20-s response–shock interval. The right-hand panels display the effects of CBZ on positively reinforced responding ($n = 5$). The task was a VI 30-s schedule of food pellet delivery. The top panels show difference scores for responses per minute; the bottom panels show difference scores for the percentage of avoided shocks (negative reinforcement) or the number of pellets delivered (positive reinforcement). Data points represent mean difference scores and the vertical bars represent ±1 S.E.M. $*P < .02$, $**P < .01$ difference from baseline.

The protocol was approved by the Vanderbilt Animal Care and Use Committee and followed National Institutes of Health guidelines.

2.2. Apparatus

Standard operant conditioning chambers (MED Associates)—24 cm wide, 30.5 cm long, and 29 cm high—were used. Each chamber was housed in a sound-attenuating chamber. Chambers consisted of translucent plastic side panels with aluminum rear and instrument panels. Each instrument panel contained two nonretractable levers (in the left and right lower corners of the panel, respectively), a pellet receptacle (located at the bottom of the panel between the levers), a house light (located at the center top of the panel), and a sonalert (mounted behind the instrument panel). The levers extended 2.2 cm from the panel wall, were 2.2 cm wide, and required a minimum downward force of 0.25 N. The pellet receptacle extended 1 cm from the panel wall and was 0.8 cm wide and 0.8 cm deep. An electromechanical 28-V DC pellet dispenser provided standard 45-mg Noyes food pellets (improved Formula A). The houselight was a 28-V DC bulb. Floors consisted of 19 stainless steel rods (4.8 mm in diameter, spaced 1.6 cm apart). A constant current shock generator and scrambler delivered 1-mA shocks, 0.5 s in duration. White noise generators supplied 80 dB sound to the experimental room. All events in the operant chamber were controlled by MED Associates software run on a MSDOS-based personal computer.

2.3. Procedure

2.3.1. Negative reinforcement analysis

Sessions, lasting 50 min, were conducted at the same time each day, 5 days/week. Houselight illumination marked the start of each session and continued throughout the session. A free-operant avoidance task (Sidman, 1953) was in effect from the beginning of the first session. A shock occurred every 5 s (shock–shock interval) until a left lever press occurred. Each subsequent left lever press

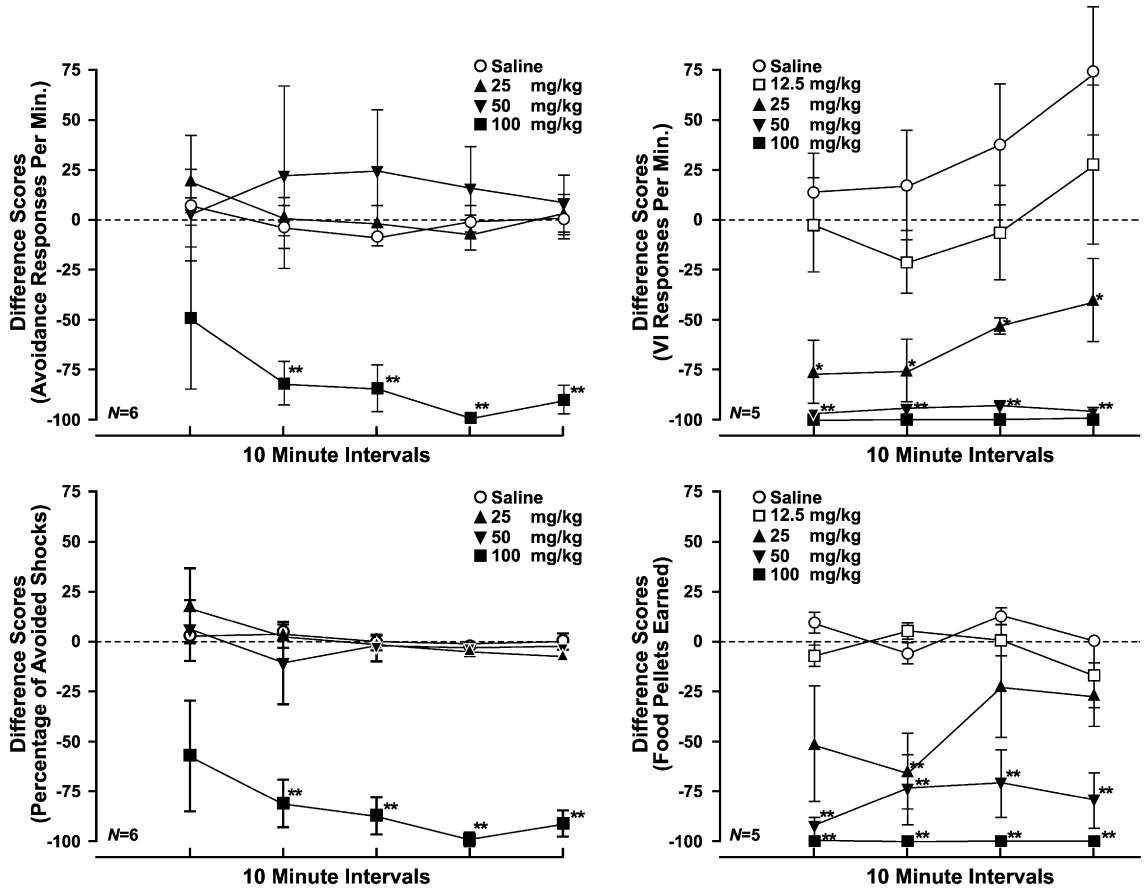

Fig. 2. Within-session analysis of the effects of different doses of CBZ (vehicle, 25, 50, and 100 mg/kg) on behavior. The left-hand panels display the effects of CBZ on negatively reinforced responding ($n=6$). The task was a free-operant procedure with a 5-s shock–shock interval and a 20-s response–shock interval. The right-hand panels display the effects of CBZ on positively reinforced responding ($n=5$). The task was a VI 30-s schedule of food pellet delivery. The top panels show difference scores for responses per minute; the bottom panels show difference scores for the percentage of avoided shocks (negative reinforcement) or the number of pellets delivered (positive reinforcement). Data points represent mean difference scores and the vertical bars represent ±1 S.E.M. difference from baseline. $*P<.02$, $**P<.01$ difference from baseline.

postponed the next shock for 20 s (response–shock interval). Throughout the experiment, data were collected separately for the first 10 min of each session ("warm-up" period) and the remaining 40 min (experimental period). Only data from the experimental period were used in the analysis. Baseline sessions continued until a stable pattern of responding and avoidance was established (+10% of previous five baseline sessions). Stability was reestablished before each experimental manipulation.

2.3.2. Positive reinforcement analysis

Lever pressing was shaped by differential reinforcement of successive approximations. Any left lever press by the animal resulted in delivery of a food pellet. Following shaping, animals were trained to lever press on a VI 30-s schedule (range: 2–104 s) of food pellet delivery. One session was run per day, 5 days/week, and lasted for 40 min. A session began with the onset of houselight illumination, which continued throughout the session. Baseline sessions continued until a stable pattern of responding and food pellet delivery was established (±10% of previous five baseline sessions). Stability was reestablished before each experimental manipulation.

2.4. Drug preparation and administration

CBZ was obtained from Sigma (St. Louis, MO) and dissolved in saline in a volume of 1 ml/kg. For the negative reinforcement analysis, an ascending dose–effect function was obtained for each animal (vehicle, 25, 50, and 100 mg/kg ip). For the positive reinforcement analysis, an ascending dose–effect function was also obtained (vehicle, 12.5, 25, 50, and 100 mg/kg ip). All injections were given 15 min prior to the start of a session.

2.5. Statistical analyses

To equate for unequal baseline responding on the negative and positive reinforcement schedules, the dependent variables were transformed into difference scores (see Figs. 1 and 2). Drug effects were tested for statistical significance using repeated-measures analysis of variance (ANOVA) with post hoc comparisons using Student's *t* tests. All post hoc tests compared drug dosage against baseline levels. Significance levels are noted in the text and figures.

Table 1
Baseline performances for the negative reinforcement analysis

Animal	Mean responses per minute	Mean percentage of avoided shocks
166	11.8	93
167	5.9	86
168	5.9	87
170	3.2	69
173	7.5	87
177	6	92
Group mean	6.7	86
Group S.E.M.	1.2	4

Table 2
Within-session baseline performances for the negative reinforcement analysis

Animal	Mean responses per minute				
	0–10 min	11–20 min	21–30 min	31–40 min	41–50 min
166	11.2	12.7	11.6	11.4	11.3
167	6.3	6	6.1	5.8	5.6
168	3.7	5.5	5.9	6.1	5.9
170	1	2.1	2.8	3.7	4.1
173	6.2	7.4	7.7	7.1	7.7
177	4	5.7	5.7	6	6.7
Group mean	5.4	6.6	6.6	6.7	6.9
Group S.E.M.	1.4	1.4	1.2	1	1

Data are arrayed as responses per minute in 10-min blocks.

3. Results

3.1. Negative reinforcement analysis

Table 1 shows baseline responses per minute and percentage of shocks avoided for the negative reinforcement analysis. Data are displayed for the last 40 min of a session. Difference scores computed from the data in Table 1 were used to compare baseline performances with responding under different levels of drug administration (Fig. 1). The top left-hand panel of Fig. 1 shows that responses per minute on the free-operant avoidance procedure were decreased by CBZ injections at the 100-mg/kg dosage [$F(5,28)=10.06$, $P<.01$]. The bottom left-hand panel of Fig. 1 shows that the percentage of shocks avoided on the free-operant avoidance procedure was decreased by CBZ injections of 100 mg/kg [$F(5,28)=69.07$, $P<.01$].

A within-session analysis of the effects of CBZ on avoidance responding is shown in Fig. 2. Baseline performances (Tables 2 and 3) were compared with responding

Table 3
Within-session baseline performances for the negative reinforcement analysis

Animal	Percentage of avoided shocks				
	0–10 min	11–20 min	21–30 min	31–40 min	41–50 min
166	89.8	94.3	91.9	93.6	91.5
167	77.1	82.9	84.3	86.4	89
168	68.6	81.8	85.9	87.1	92.4
170	27.6	52	65.3	75.4	81.3
173	76.3	84.6	86.5	87.9	88.9
177	74.6	88.4	92.1	92.4	93.8
Group mean	69	80.7	84.3	87.1	89.5
Group S.E.M.	8.8	6	4	2.6	1.8

Data are arrayed as percentage of shocks avoided in 10-min blocks.

Table 4
Baseline performances for the positive reinforcement analysis

Animal	Mean responses per minute	Mean number of food pellets per minute
169	26.1	1.7
172	37.8	1.7
174	35.2	1.7
175	26.6	1.7
176	31.6	1.7
Group mean	31.5	1.7
Group S.E.M.	2.3	0.1

under different levels of drug administration to derive difference scores in 10-min blocks (Fig. 2). The data in the top left-hand panel show significant differences only for CBZ injections at the 100-mg/kg dosage level [$F(5,28) = 14.43$, $P < .01$]. Similar results for CBZ were obtained for the percentage of shocks avoided [$F(5,28) = 101.2$, $P < .01$]. Fig. 2 also shows that the performance of the animals was consistent across the length of the session for responses per minute and percentage of avoided shocks.

3.2. Positive reinforcement analysis

Table 4 shows baseline responses per minute and food pellet deliveries per minute for the positive reinforcement analysis. Data are displayed for 40-min sessions. Difference scores computed from the data in Table 4 were used to compare baseline performances with responding under different levels of drug administration (Fig. 2). The top right-hand panel of Fig. 2 shows that response rates on the VI 30-s schedule of reinforcement linearly decreased following CBZ injections of 25, 50, and 100 mg/kg [$F(4,28) = 9.11$, $P < .02$]. The bottom right-hand panel of Fig. 1 shows that the number of food pellet deliveries per minute linearly decreased following CBZ injections of 25, 50, and 100 mg/kg [$F(4,28) = 15.22$, $P < .01$].

A within-session analysis of the effects of CBZ on VI 30-s schedule performance is shown in Fig. 2. Baseline performances (Tables 5 and 6) were compared with responding under different levels of drug administration to derive difference scores in 10-min blocks (Fig. 2). The data in the top left-hand panel show significant differences for CBZ injections at the 25-, 50-, and 100-mg/kg dosage level [$F(4,28) = 11.1$, $P < .01$]. CBZ produced similar results for the number of food pellets delivered per minute [$F(4,28) = 9.24$, $P < .01$]. Both right-hand panels in Fig. 2 show dose-dependent effects on behavior. The effects of CBZ on behavior was consistent across the length of the session at higher dosages (i.e., 50 and 100 mg/kg), but decreased with session length at 25 mg/kg.

Table 5
Within-session baseline performances for the positive reinforcement analysis

Animal	Mean responses per minute			
	0–10 min	11–20 min	21–30 min	31–40 min
169	23.8	29.4	26.6	22.4
172	33.4	43.7	38.4	31.4
174	35.5	40.6	38	26.9
175	20.5	33.2	28.4	18.3
176	31.4	38.7	31.7	24.2
Group mean	28.9	37.1	32.6	24.6
Group S.E.M.	2.9	2.6	2.4	2.2

Data are arrayed as responses per minute in 10-min blocks.

Table 6
Within-session baseline performances for the positive reinforcement analysis

Animal	Mean food pellets per minute			
	0–10 min	11–20 min	21–30 min	31–40 min
169	1.8	1.7	1.7	1.6
172	1.6	1.9	1.8	1.7
174	1.9	1.7	1.8	1.7
175	1.6	1.7	1.8	1.6
176	1.7	1.9	1.7	1.5
Group mean	1.7	1.8	1.7	1.6
Group S.E.M.	0.05	0.05	0.02	0.04

Data are arrayed as responses per minute in 10-min blocks.

4. Discussion

We analyzed the effects of CBZ on negatively versus positively reinforced responding. CBZ did not change the rate of responding or the percentage of shocks avoided on the free-operant avoidance task except at 100 mg/kg. At this level, responding and avoided shocks were decreased by approximately 90% of baseline levels. CBZ gradually decreased rates of responding and food pellets earned on the VI schedule beginning at 25 mg/kg in a dose-dependent fashion. These findings indicate that CBZ has differential effects on avoidance versus appetitively maintained operant behavior.

Our findings differ from those previously reported for CBZ. Previous experiments with rats and mice have indicated that CBZ decreases the acquisition of negatively reinforced avoidance behavior. In relation to our data, the findings of Banks et al. (2001) and Voigt and Morgenstern (1992) appear to be related to response acquisition rather than negative reinforcement. The only effect we observed on avoidance responding for CBZ was at the point of general sedation. Therefore, it appears likely that the effects of previous research may be due either to disruptions in response acquisition or general sedation.

Previous research analyzing the effects of CBZ on positively reinforced responding has shown little effect. In a study by Evenden and Ryan (1996), CBZ did not disrupt performances on a delayed reinforcement task, although benzodiazepines and *d*-amphetamine did alter responding. Our findings demonstrated a dose-dependent decrease in appeti-

tively maintained responding. That effect was observed with dosages as low as 25 mg/kg in our experiment, even though Evenden and Ryan used dosages of 40 and 100 mg/kg. Two procedural explanations are possible. First, the route of administration differed in the two studies (intraperitoneal in our experiment versus per orem in the Evenden and Ryan experiment). Research has shown that the pharmacokinetics associated with routes of administration differs for CBZ, with intraperitoneal drug administration producing effects at lower dosages than per orem administration (Nakao et al., 1985; Rogawski et al., 1991). A second possible explanation is the type of operant task required of the animals. The VI schedule used in the current experiment produces response rates with longer interresponse times, whereas the delayed choice procedure used by Evenden and Ryan produces bursts of responding with short interresponse times. It is possible that these differences in the quantal nature of the responding produced on the two appetitive reinforcement schedules contributed to the differing effects.

Our results clearly showed differences in the effects CBZ had on negatively versus positively reinforced behavior. However, we established only one type of operant performance for each of these qualitatively different reinforcers. We chose free-operant avoidance and VI appetitive reinforcement schedules because they have been extensively studied in the behavioral psychopharmacology literature and have shown sensitivity to psychoactive compounds (Thompson and Boren, 1977). Future research will be needed to establish the robustness of our findings across a broader range of operant reinforcement schedules.

The comparison of qualitatively different operant reinforcement schedules presents interpretative difficulties that should be noted. Optimally, parameters of the negative and positive reinforcement schedules would be adjusted so that similar response rates and interresponse times were established on each schedule. Therefore, it is possible that our results may have been influenced by differences in response rates and/or interresponse times. In addition, the avoidance schedule was response-based and the appetitive schedule was time-based, making it possible that schedule dynamics may have influenced the differential effects of CBZ on responding. We chose to use free-operant avoidance and VI appetitive schedules because they have been extensively characterized in the behavioral pharmacology literature and shown to be sensitive to a range of psychoactive compounds. However, future research focusing on how CBZ affects qualitatively different reinforcers should consider response rate, schedules parameters, and reinforcer magnitude, in addition to drug dosage.

Finally, we would like to note some applied implications of our findings. Our interest in CBZ and other AEDs derives from clinical issues relating to developmental disabilities. CBZ is often prescribed to people with developmental disabilities to control self-injury and aggression relating either to epilepsy or impulse control problems. Currently, it is unclear whether the mechanism of action for reducing self-injury or aggression using CBZ is via a selective alteration in neural circuits or through general sedation (Kennedy and Meyer, 1998). Of particular relevance to the current experiment is that approximately 70% of self-injury or aggression cases can be identified as being maintained by positive and/or negative reinforcers (Derby et al., 1992; Iwata et al., 1994). If our findings can be extrapolated to this literature, our experimental results suggest that CBZ may be an indicated pharmacological treatment for self-injury and aggression maintained by positive reinforcement, but not for behavior maintained by negative reinforcement. Whether this is the case awaits future research linking psychopharmacotherapy and behavioral analyses of self-injury and aggression (Kennedy et al., 2001).

Acknowledgements

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