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Effects of Valproic Acid and Ethosuximide on the Responding of Pigeons Maintained Under a Multiple Fixed-Ratio Fixed-Interval Schedule of Food Delivery[1]

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POLING, A., M. PICKER, D. GROSSETT AND D. VANDE POLDER. *Effects of valproic acid and ethosuximide on the responding of pigeons maintained under a multiple fixed-ratio fixed-interval schedule of food delivery.* PHARMACOL BIOCHEM BEHAV **23**(3) 469–472, 1985.—The effects of valproic acid and ethosuximide were examined in pigeons responding under a multiple Fixed-Ratio 50 Fixed-Interval 90-sec schedule of food delivery. When given acutely 30 min prior to behavioral testing, both valproic acid (40, 60, 80, 100, and 120 mg/kg) and ethosuximide (40, 60, 80, 100, and 120 mg/kg) produced generally dose-dependent decreases in responding under both the Fixed-Ratio and Fixed-Interval components. Detailed analysis of drug effects on the temporal distribution of responding under the Fixed-Interval failed to reveal rate-dependent effects for either drug. Varying the presession injection interval from 15 to 120 min indicated that both valproic acid and ethosuximide reduced responding to the greatest extent when given 30 or 60 min before behavioral testing. These results indicate that the anticonvulsants valproic acid and ethosuximide similarly affect schedule-controlled responding, although previous studies have revealed the drugs to have different effects under other procedures.

Valproic acid Ethosuximide Multiple schedule Pigeons Fixed-ratio schedule Fixed-interval schedule

IT has been known for over 50 years that anticonvulsant drugs can contribute to mental deterioration and learning problems in epileptic individuals. However, clinical investigations examining the behavioral effects of anticonvulsant drugs have yielded inconclusive results (see [2]). Further, methodological shortcomings render the findings of many such studies uninterpretable. Given this, and the difficulties inherent in conducting clinical drug research with humans [10], it is not surprising that investigations of the behavioral effects of anticonvulsant drugs in nonhuman subjects have begun to appear (e.g., [3, 6, 7, 8]).

Recent investigations have indicated that different anticonvulsant drugs, including valproic acid and ethosuximide, produce dissimilar behavioral effects in pigeons responding under delayed-matching-to-sample and repeated acquisition procedures [6,8]. Under these procedures, valproic acid appreciably increased errors, but ethosuximide failed to have such an effect.

The purpose of the present study was to further profile the behavioral actions of ethosuximide and valproic acid by determining their effects on the schedule-controlled behavior of pigeons. Studies of the effects of drugs on schedule-controlled behavior have yielded a wealth of information about many drug classes (see [4,9]), but no comparisons of the effects of ethosuximide and valproic acid on schedule-controlled responding have appeared. However, previous studies have shown that other anticonvulsants (e.g., phenytoin and phenobarbital) which produce different effects under the delayed-matching-to-sample procedure differ greatly with respect to their effects on schedule-controlled behavior [1, 3, 5].

METHOD

Subjects

Six experimentally-naive White Carneaux pigeons, maintained at 80% of free-feeding weights, served as subjects. Each bird was individually housed with unlimited access to grit and water in a constantly illuminated room.

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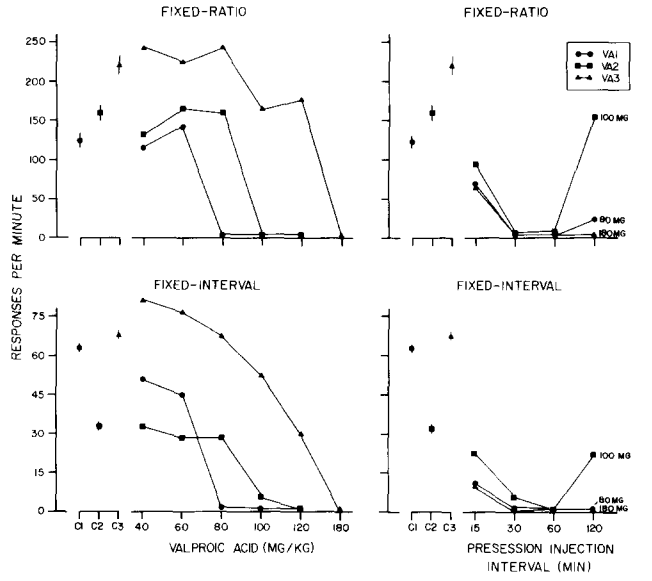

FIG. 1. Effects of acute administrations of valproic acid on the response rates of individual pigeons performing under a mult FR 50 FI 90-sec schedule of food delivery. The top row of panels depict responding under the FR component, the bottom row responding under the FI component. Panels on the left show rate of responding when five doses of valproic acid were administered IM 30 min prior to the start of behavioral testing. Panels on the right show the effects of one dose of valproic acid injected IM at various times prior to behavioral testing. The dose given to each subject (indicated in the figure) reduced rate of responding under the FR component by a minimum of 50% when administered 30 min prior to the session. Control data for all panels (C1, C2, C3) are expressed as the mean response rate for the three sessions immediately prior to all drug administrations; vertical lines indicate the standard error of the mean.

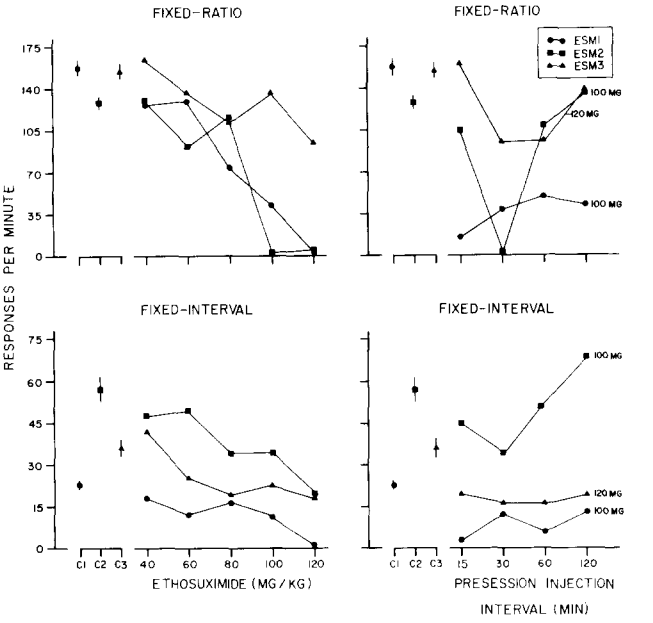

FIG. 2. The effects of acute administrations of ethosuximide on the response rates of individual pigeons performing under a mult FR 50 FI 90-sec schedule of food delivery. Details are as described in Fig. 1.

Apparatus

Three Lehigh Valley Electronics (BRS/LVE, Lehigh Valley, PA) operant conditioning chambers, measuring 32 cm long, 36 cm high, and 35 cm wide, were employed. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the intelligence panel, approximately 5.5 cm apart; only the center key was employed in the present study. This key could be illuminated in blue or red, and a minimum of 0.2 g pressure was required for key operation. An aperture horizontally centered on the intelligence panel 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. A 7-W bulb centrally mounted 33 cm above the chamber floor provided ambient illumination, and a fan provided masking noise and ventilation.

Scheduling of experimental events and data collection were accomplished through the use of a PDP8/A minicomputer (Digital Equipment Corp., Maynard, MA) using interfacing and software (SUPERSKED) provided by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

After initial keypeck training, subjects were exposed to a multiple Fixed-Ratio 50 Fixed-Interval 90-sec (mult FR 50 FI 90-sec) schedule of food delivery. Under this schedule, the color of key illumination alternated at 5-min intervals. An FR 50 schedule was always in effect when the key was red, whereas an FI 90-sec schedule was arranged when the key was blue. Under the former schedule, a 3-sec food delivery followed every fiftieth keypeck. Under the latter, 3-sec of food delivery followed the first response emitted at least 90 sec from the previous food delivery, or from the onset of blue key illumination. Throughout the study, sessions were 30 min in duration and always began with blue key illumination (i.e., with the FI component in effect). Sessions were conducted 6 days per week, at about the same time each day.

Pharmacological Procedure

Dose-response testing. When all subjects evidenced stable response rates (i.e., no visually evident trend over 10 consecutive sessions) under both components of the mult FR 50 FI 90-sec schedule, they were randomly divided into 2 groups of 3. One group received ethosuximide, the other valproic acid. Five doses of ethosuximide (Warner-Lambert, Ann Arbor, MI) were evaluated. These doses, selected on the basis of prior findings from our laboratory [6,8] were 40, 60, 80, 100, and 120 mg/kg. Each bird received each dose once, in an irregular order that differed across subjects. Ethosuximide was dissolved in isotonic saline solution and injected intramuscularly (IM) 30 min prior to the session at a volume of 1 ml/kg (pH about 7.5). Active drug was given only when responding in both components of the mult schedule was stable (i.e., showed no visually evident trend) over 3 consecutive sessions, at least one of which involved IM injection of 1 ml/kg isotonic saline solution 30 min prior to the session.

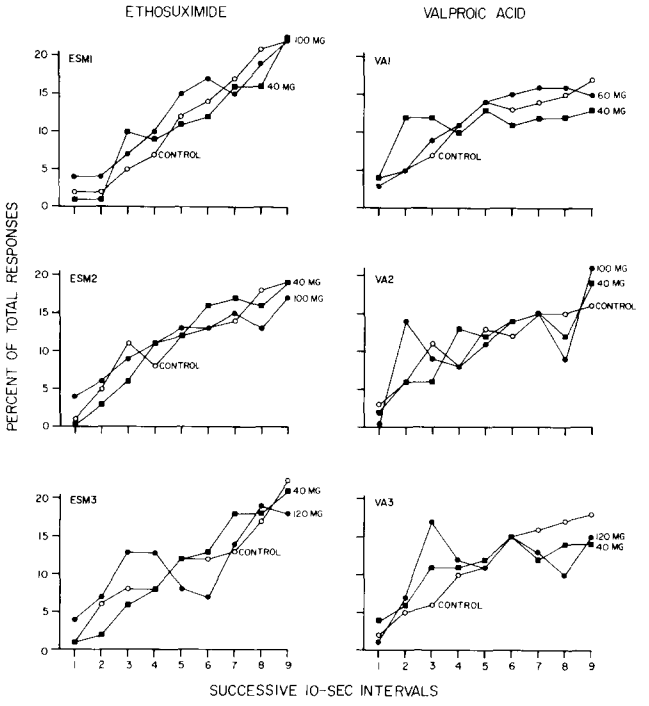

FIG. 3. Effects of selected doses of valproic acid and ethosuximide on the percent of total responses emitted during successive 10-sec intervals of the FI 90-sec component. Open circles indicate performance during a representative saline control session. Squares show performance when the lowest dose of valproic acid (right panels) or ethosuximide (left panels) was administered. Closed circles indicate the temporal distribution of responding when a relatively high dose of valproic acid or ethosuximide was administered. For each bird, this high dose was that at which responding under the FI occurred at the lowest nonzero rate.

TABLE 1

EFFECTS OF VALPROIC ACID AND ETHOSUXIMIDE ON RUN RATES AND POSTREINFORCEMENT PAUSE TIMES UNDER THE FIXED-RATIO COMPONENT

Subject	0*	40	60	80	100	120	180
			Run Rates (Responses/Min)				
			Valproic Acid (mg/kg)				
VA1	179(3)	172	186	0	0	0	—
VA2	218(3)	185	224	220	3	0	—
VA3	336(4)	365	316	367	320	309	0
			Ethosuximide (mg/kg)				
ESM1	249(6)	213	232	151	123	2	
ESM2	183(2)	187	159	160	0	4	
ESM3	215(3)	211	192	155	194	126	
			Postreinforcement Pause Times (Sec)				
			Valproic Acid (mg/kg)				
VA1	5.3(0.5)	5.5	2.1	—	—	—	—
VA2	2.3(0.2)	3.2	2.0	1.7	—	—	—
VA3	2.1(0.2)	1.3	1.1	1.3	5.8	4.4	—
			Ethosuximide				
ESM1	4.5(0.2)	6.4	6.9	16.0	42.0	—	
ESM2	4.5(0.2)	4.4	12.2	4.6	—	—	
ESM3	2.8(0.3)	1.1	3.5	5.3	3.6	5.5	

*Control values represent the mean (and one standard error) for all sessions which immediately preceded drug administrations.

†Postreinforcement pause times represent the mean time that elapsed from the offset of food presentation to the emission of a keypeck.

Five doses of valproic acid (Saber Laboratories, Morton Grove, IL), selected on the basis of prior findings from our laboratory [6, 7, 8], also were evaluated. These doses were 40, 60, 80, 100, and 120 mg/kg, injected IM 30 min prior to the session. (One subject, VA3, was little affected by these doses and hence was tested with 180 mg/kg.) Valproic acid was dissolved in isotonic saline solution with sufficient sodium hydroxide added to neutralize the drug to the sodium salt, and was injected at a 1 ml/kg volume (pH about 9.0). As with ethosuximide, doses of valproic acid were administered in an irregular order, and active drug was given only when responding was stable across the 3 preceding control sessions, at least one of which was preceded by injection of isotonic saline solution.

Time-course determination. Following initial dose-response determinations, the effects of presession injection interval were assessed. In this phase of the study, subjects received a single dose of ethosuximide or valproic acid at presession injection intervals of 15, 60, and 120 min. The dose administered to an individual bird was the lowest one which reduced responding in the FR component of the mult schedule by at least 50% during initial dose-response testing. Conditions of drug administration during the time-course determination were identical to those in effect for dose-response testing.

RESULTS

During each session, response rates in the FR and FI components were recorded. In addition, for the FR component, mean postreinforcement pause times (i.e., average elapsed time from the completion of one FR 50 to emission of the next response) and running rates (i.e., total responses/total time—postreinforcement pause time and latency to respond when conditions changed) were recorded. For the FI component, the number of responses emitted in each of nine consecutive 10-sec segments of the FI 90-sec was recorded; this measure was taken to allow for an assessment of possible rate-dependent drug effects.

The effects of acute administrations of valproic acid and ethosuximide are shown in Figs. 1 and 2, respectively. As indicated in the left frames of these figures, when administered 30 min prior to the session each of these drugs produced generally dose-dependent decreases in responding under both the FR and FI components of the mult schedule. The right frames of these figures further indicate that the largest decreases in rates of responding were evidenced at the 30 and 60 min presession injection intervals.

Figure 3 shows the effects of selected doses of each drug on the temporal distribution of responding under the FI component. Control data indicate that, in the absence of

drug, each bird responded at a higher rate as the FI progressed. This characteristic pattern was not systematically affected by either valproic acid or ethosuximide; although overall response rate was frequently lowered by the drugs, this did not alter the relative allocation of responses across the FI. Such an outcome suggests that neither drug produced rate-dependent effects.

Data presented in Table 1 indicate that under the FR component valproic acid slightly increased or failed to affect mean running rates at low doses, and strongly reduced mean running rates at high doses. Valproic acid's effects on mean postreinforcement pause times were inconsistent. Ethosuximide produced generally dose-dependent decreases in mean running rates. This drug also typically increased mean postreinforcement pause times, although the magnitude of this effect was not obviously dose-dependent.

DISCUSSION

Valproic acid and ethosuximide have been demonstrated to have dissimilar actions under repeated acquisition and delayed-matching-to-sample procedures [6,8], where only the former drug increased errors. Despite this, the two drugs affected schedule-controlled behavior similarly in the present study. With each, the primary effect observed was a nonselective, and generally dose-dependent, decrease in response rates under both FR and FI schedules. Although rate-dependent effects have been reported for many drugs [4,9], including the anticonvulsant phenobarbital [1,5], the effects of both valproic acid and ethosuximide in the present study appeared to be independent of control (i.e., nondrug) response rates, as were the effects of valproic acid in an earlier investigation [7]. That neither drug produced clearly rate-dependent effects in the present study is suggested by the observation that (a) drug effects were similar under the FR and FI components, even though the former engendered a considerably higher nondrug response rate, and (b) neither drug systematically affected the temporal distribution of responses under the FI component.

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