Pharmacology Biochemistry and Behavior, Vol. 63, No. 3, pp. 465–472, 1999

0091-3057/99/ $–see front matter

ELSEVIER

PII S0091-3057(99)00019-2

The Effects of Phenytoin on Instrumental Appetitive-to-Aversive Transfer in Rats

M. K. BANKS,*† N. L. MOHR,* J. BESHEER,* J. E. STEINMETZ*† AND P. E. GARRAGHTY*†

Department of Psychology, †Program in Neural Science, Indiana University Bloomington, IN 47405

Received 4 September 1998; Revised 15 December 1998; Accepted 22 December 1998

BANKS, M. K., N. L. MOHR, J. BESHEER, J. E. STEINMETZ AND P. E. GARRAGHTY. *The effects of phenytoin on instrumental appetitive-to-aversive transfer in rats.* PHARMACOL BIOCHEM BEHAV **63**(3) 465–472, 1999.—Antiepileptic medications are the primary treatment for seizure conditions. Over the past several years, it has become clear that the medications themselves may contribute to the negative cognitive side effects that people with epilepsy often report. In the experiments reported here, the effects of phenytoin treatment have been evaluated in rats performing an instrumental appetitive-to-aversive transfer task. We find that rats treated with phenytoin fail to acquire the avoidance response when transferred from an appetitive to an aversive context. This deficit is not due to any sensory or motor slowing resulting from the drug, nor is it a deficit that is specific to learning in an aversive context. Rather, we suggest that the deficits shown by phenytoin-treated rats in the appetitive-to-aversive transfer reflect a fundamental inability in altering the associations that were formed during the initial appetitive training. © 1999 Elsevier Science Inc.

Dilantin© Avoidance learning Epilepsy Antiepileptic drugs Anticonvulsants

EPILEPSY is a family of central nervous system disorders, characterized by neuronal hyperactivity resulting in seizures, afflicting as many as 2.5 million people in the United States alone. For nearly 140 years, pharmacological intervention has been the treatment of choice. In 1908, diphenylhydantoin sodium (phenytoin; PHT) was synthesized, but it was 30 years later that Merritt and Putnam (26) first demonstrated its anticonvulsant properties (32). Phenytoin quickly became the drug of choice for the treatment of epilepsy as this drug appeared to control seizures effectively without the obviously soporific side effects associated with the available treatment options (i.e., bromides and phenobarbital).

Phenytoin, however, may not control seizure activity without unwanted side effects. For example, "cognitive" deficits have been associated with phenytoin maintenance in human patients [e.g., (12,15,19,24,30,31,34,35,36,38–40,42,45) and in animal models [e.g., (21,29,43)]. These reports of cognitive and behavioral impairments have not gone completely unchallenged. Echoing the concerns raised by others [see (3,11,41,44) for discussion], Dodrill (16) has argued that recent data show that phenytoin, carbamazepine, and valproate have only mildly adverse effects, and that the effects due to these compounds were comparable. Dodrill (16) goes on to list a number of reasons (e.g., subject selection factors, comedication, particular psychological test employed) why earlier results might have been interpreted as indicative of more severe drug-related effects. The bottom line, however, remains the same. There have been no systematic assessments of the relative degrees of impairment associated with various antiepileptic compounds. The experiments reported here represent our initial studies of the effects of phenytoin maintenance on learning and memory in adult rats. We have employed a within-subject, tone-signaled bar press task in which rats are transferred from an appetitive to an aversive context. This paradigm was developed to study appetitive and aversive learning in the same subjects, and has been used in past work to evaluate learning, memory, and impairments that accompany cerebellar, hippocampal, cingulate, and prefrontal cortex lesions (23,37). We are currently using this paradigm to study the effects of a number of other compounds (carbamazepine, valproate, ethosuximide, and felbamate thus far), and the preliminary results show that this paradigm does discriminate between these various drugs. In the present study, we found that phenytoin-treated rats were severely im-

Requests for reprints should be addressed to Preston E. Garraghty, Program in Neural Science, Department of Psychology, Indiana University, Bloomington, IN 47405.

paired in the acquisition of the avoidance response relative to normal controls. Preliminary reports of some of these findings have appeared elsewhere (5–7,27).

METHOD

Subjects and Materials

Forty-seven adult female Sprague–Dawley rats bred in the Indiana University animal care facilities were used. The animals were maintained at 85% free-feeding body weight throughout their participation in the study. The 45-mg food pellets used as appetitive reinforcers (Bio-Serve, Frenchtown, NJ) were introduced to the animals in the home cage at least 2 days prior to beginning training. Animals were trained in an operant chamber (Lafayette) placed in a lighted (10-W utility bulb) sound-attenuating chamber, which contained a center-mounted speaker to deliver the tone (2 kHz at 90 dB SPL). The front wall of the operant box consisted of one bar at center and a recessed food well on the left.

Surgeries

All animals (n = 47) underwent a simple surgical procedure to implant two back wires, necessary as the connection point for the active lead during the aversive component of the task, before beginning shaping and training for the first (or only) component. Animals were anesthetized with a mixture of ketamine and xylazine (60 and 6 mg/kg, respectively, IM), with supplemental doses given as needed. Two double-loop wires (30 gauge surgical), approximately 1 cm apart, were threaded subcutaneously between the scapulae of each animal. Animals also received 0.2 cc Dopram (IM) and triple antibiotic ointment on the area of the wires. The entire procedure took approximately 15 min per subject.

Drug Administration

The antiepileptic medication phenytoin (Dilantin; Parke-Davis, Morris Plains, NJ) was administered as stated in the detailed methods for each experimental condition. The phenytoin oral suspension (125 mg/5 ml) was administered to each animal via gavage twice daily. The dose level employed in the experiments was determined using a regimen of plasma assay testing after 10 and 35 days of phenytoin treatment. Two hours after the last dosing (comparable to when the animals are drugged and then perform the task), 1 cc of blood was obtained from a number of animals, and assayed for phenytoin concentration by an outside technician. From the plasma concentration assay, a dose nearly 10 times (50 mg/kg/day) that required for humans was needed to approximate the low end of the human therapeutic concentration level (10–20 μg/ml).

Appetitive-to-Aversive Transfer Task

Appetitive context. All sessions, appetitive or aversive, were separated by 24 h. In the appetitive context, the animals were first shaped using a method of successive approximations to the bar press behavior for food reinforcement. When the animal pressed the bar 100 times in 30 min on a continuous reinforcement schedule, they were advanced to a partial reinforcement schedule (FR4) to strengthen the behavior (i.e., render it more resistant to extinction). They were then required to perform 400 bar presses (receive 100 pellets) within 30 min on two consecutive days before they began the tone training trials. During the tone-signaled sessions, the rat had to press the bar during the tone to receive the reward. One session consisted of a total of 100 tones, each lasting 3 s or until the food pellet was delivered, followed by a 15-s intertrial interval (ITI) and a randomly determined 1–8-s pretone period. If the rats pressed the bar during this pretone period, the period was reset and the trial was delayed until no bar presses occurred during the randomly determined pretone period. Animals continued appetitive tone training for a total of 31 days.

Aversive context. The rats were then transferred to an active avoidance task. The aversive context consisted of a shock that could be terminated by a bar press. The shock intensity was usually maintained at 0.7 mA. If the animal did not respond well to the shock level, it was increased slightly until a level was found at which the animals responded consistently, but never to exceed 1.0 mA. The animals were introduced to the aversive context in a single training session where the shock pulses were presented continuously until the bar was pressed. If the animal did not press the bar within 30 pulses, the current was turned off manually for a rest period of 10 s. When the animal pressed the bar, a rest period of 30 s was initiated. The subject was required to press the bar prior to the onset of the fifth shock pulse at least 15–20 times consecutively, and was advanced to tone trials on the next session day. The tone was the same used in the appetitive condition (2 kHz, 90 dB SPL). On tone-signaled trials, the impending foot shocks could be avoided by a bar press during the first 3 s of tone presentation, or escaped by a bar press in the latter 3 s after the shock was initiated. The shock was delivered as a series of four 250-ms pulses separated by 500-ms periods of no shock. To prevent the animals from adopting a strategy of holding the bar down for excessive amounts of time (thereby avoiding the shock), continuous shock pulses were delivered if the animal failed to release the bar after 5 s. The trials were separated by 8-12 s ITIs and a variable 2–6 s pretone period, during which a bar press reset the pretone period and delayed the initiation of the next trial. One session of avoidance learning consisted of 300 tone presentations, or 300 chances to avoid or escape the shock. Tone training in the aversive phase of the experiment continued for 25 days.

Experimental Conditions

Effects of phenytoin on appetitive-to-aversive transfer. Twelve rats served as controls, receiving no gavage treatment throughout the appetitive and avoidance training. In groups of nine and six rats, administration of phenytoin or water (respectively) was initiated at the conclusion of the appetitive training session on the 21st day. These animals continued tone training for 10 days to assess the effect of the drug and/or gavage procedure, if any, on the acquired tone-signaled bar press. After the initiation of drug (or water) treatment, behavioral testing began 2 h after phenytoin (or water) administration. Drug or water treatment continued daily throughout the remaining appetitive and total number of avoidance training sessions.

Effects of phenytoin on appetitive acquisition. In a group of four rats, phenytoin treatment was initiated. After 10 days of drug delivery, the rats entered the appetitive training context. Animals underwent appetitive shaping sessions until the criteria were met, and then began appetitive tone-training sessions. All parameters remained as described above for the appetitive context. Drug treatment continued throughout the training.

Effects of phenytoin on an acquired avoidance response. Six animals completed the appetitive-to-aversive transfer task and began phenytoin maintenance after the 25th avoidance training session. Two of these animals were included in the transfer task control data. The other four animals underwent training that consisted of only 200 trials while in the aversive component of the transfer task; therefore, these animals were not included in the controls for the transfer task. These animals continued in avoidance training for 10 additional days.

Effects of phenytoin on avoidance acquisition without prior appetitive experience. Finally, in another group of 12 animals (four phenytoin-treated, four water-treated, and four untreated controls), phenytoin or water treatment was initiated, and continued for 10 days, at which time the animals began avoidance training. Animals performed one session of aversive shaping and began the 25 days of tone-signaled avoidance training the following day. All parameters in the avoidance context remained as described above, but without prior exposure to the appetitive context.

Statistics

To evaluate learning performance differences between the drug-treated and control groups (as well as between water-treated and untreated animals, when available) across training days, a repeated-measures analysis of variance model was applied (ANOVA). In general, performance across 5-day blocks were used to demonstrate performance level. Statistical decisions were based on a 0.05 significance level. The calculations were carried out using SPSS 6.0 software, on a Power Macintosh 6100.

RESULTS

Appetitive-to-Aversive Transfer: Appetitive Performance

Appetitive acquisition in controls. Figure 1 presents percentages of reinforced bar presses and efficiency ratios (ERs; reinforced bar presses/total number of bar presses) for water-treated and untreated controls. These groups have been collapsed for presentation because they did not differ for either of these measures [days 17–21: reinforced bar presses, $F(1, 16) = 1.21$, $p > 0.05$; ERs, $F(1, 16) = 1.28$, $p > 0.05$; days 27–31: reinforced bar presses, $F(1, 16) = 0.01$, $p > 0.05$; ERs, $F(1, 16) = 0.68$, $p > 0.05$]. Moreover, asymptotic performance levels for these two variables were achieved by the 17th to 21st days of behavioral training; performance levels for days 27–31 were comparable [reinforced bar presses, $F(9, 144) = 1.43$, $p > 0.05$; ERs, $F(9, 144) = 1.50$, $p > 0.05$]. On average, the performance of both the phenytoin-treated and control animals continued to improve slightly, making 1.2% more reinforced bar presses by days 27–31 than days 17–21.

Appetitive performance in phenytoin-treated rats. To determine whether phenytoin treatment had any effect on the acquired appetitive performance, we compared data from 5 days prior to the initiation of drug administration with those from the last 5 days of drug treatment in the appetitive context. Figure 1 presents percentages of reinforced bar presses and ERs for phenytoin-treated rats. Percentages of reinforced bar presses (Fig. 1A) remained stable after the initiation of phenytoin treatment, $F(9, 72) = 0.62$, $p > 0.05$. Efficiency ratios, however, did improve with the additional training, from an average of 0.508 for days 17–21 to an average of 0.618 for days 27–31, $F(9, 72) = 2.29$, $p < 0.05$.

Comparisons of phenytoin-treated rats to controls. The performance levels of the drug-treated rats were generally comparable to those of the controls. Terminal ERs were indistinguishable, $F(1, 25) = 0.05$, $p > 0.05$. On the other hand, the percentages of reinforced bar presses for training days 27–31 were significantly different, $F(1, 25) = 10.85$, $p < 0.05$, with the averages being 88.8 and 95.5% for the phenytoin-treated and control rats, respectively. It is noted that the percentages of reinforced bar presses were comparably lower for the phenytoin-treated animals (88.6%) relative to the controls (94.3%) for training days 17–21, $F(1, 25) = 5.46$, $p < 0.05$, which is before the initiation of drug treatment.

Effects of Phenytoin on Appetitive Acquisition

To evaluate the possibility that the lower terminal percentages of reinforced bar presses for the phenytoin-treated rats was due to a reduction in appetitive motivation, four rats began receiving phenytoin 10 days before appetitive shaping and tone training. The drug treatment continued throughout appetitive training. These rats averaged 96.9% reinforced bar presses over training days 27–31. The comparable average for

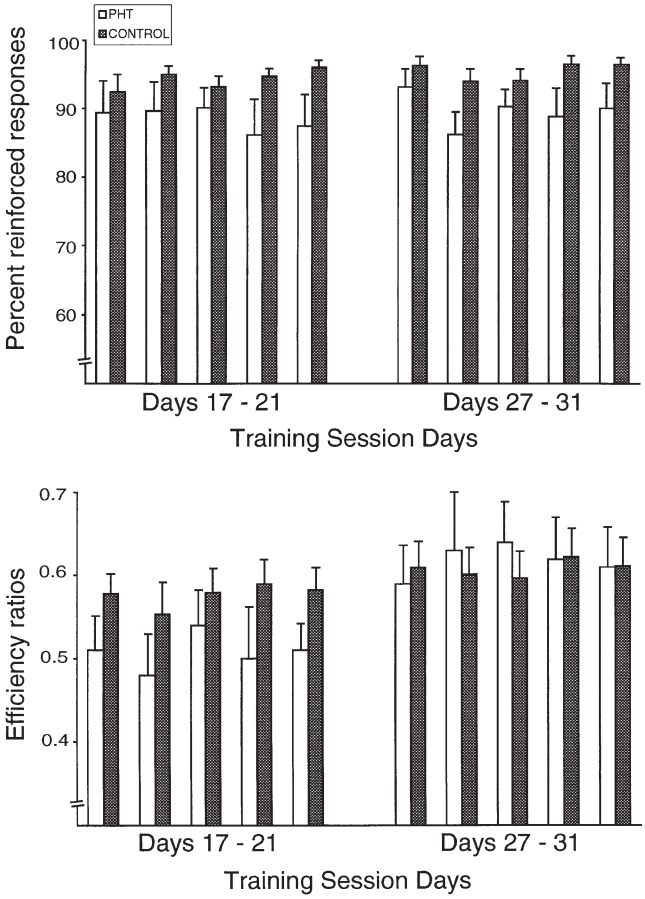

FIG. 1. Appetitive performance measures for control (water-treated and untreated combined) and phenytoin-treated animals are displayed. Percentages of reinforced bar presses and efficiency ratios for control animals demonstrate that these animals learn the appetitive task, and performance is maintained even after initiation of water treatment. Phenytoin-treated animals show no negative effect on the maintenance of appetitive performance and a slight increase in performance efficiency.

the control animals (see Fig. 1) was 95.5%, $F(1, 20) = 0.36$, $p > 0.05$. Similarly, the ERs for the phenytoin-treated animals for training days 27–31 of the appetitive context were comparable to those of the control animals, $F(1, 20) = 0.02$, $p > 0.05$.

Appetitive-to-Aversive Transfer: Avoidance Performance

Acquisition. Following appetitive training, the rats were transferred to avoidance training. Figure 2 presents the percent avoidances for the first and last 5 days of training for the phenytoin-treated and control rats (water treated and untreated). Data from the latter two groups have been collapsed in this figure because the avoidance performance found in the water-treated and untreated rats was comparable [days 1–5: $F(1, 16) = 1.14$, $p > 0.05$; days 21–25: $F(1, 16) = 0.04$, $p > 0.05$]. Overall, the phenytoin-treated rats avoided at significantly lower rates than the controls across the first 5 days of training, $F(1, 25) = 20.79$, $p < 0.05$. By the fifth day, controls were averaging 51% avoidances, while the drug treated animals averaged only 8.1%.

Terminal performance. Over the last 5 days of avoidance training, the average avoidance rate for the controls was 64.0%. Phenytoin-treated animals averaged significantly fewer avoidances (20.5%) over these same training days, $F(1, 25) = 17.0$, $p < 0.05$. Thus, the control animals improved steadily, plateauing in excess of 60% on average by the last 5 days of training. In contrast, the average avoidance rate never exceeded 23% on any of the training days for the phenytoin-treated rats.

Efficiency ratios. The ERs (efficiency ratios: avoidances/total number of bar presses) on the first and the last 5 days of aversive training for the control and phenytoin-treated rats are presented in Fig. 2. Whereas both groups were relatively inefficient on the first day of training, the control rats showed steady improvement while the phenytoin-treated rats did not. The ERs of the water-treated and untreated controls were again statistically comparable, and the data were collapsed [days 1–5: $F(1, 16) = 0.63$, $p > 0.05$; days 21–25: $F(1, 16) = 0.04$, $p > 0.05$]. In contrast, the ERs of the drug-treated rats were significantly lower than those of the controls over the first 5 days of training, $F(1, 25) = 8.27$, $p < 0.05$. While the drug-treated animals show some improvement over training, their average ER for the last 5 days of training (0.091) was significantly lower that those of the control groups [0.400; $F(1, 25) = 14.61$, $p < 0.05$].

Effects of Phenytoin on Acquired Avoidance Responding

Figure 3 presents percent avoidances and ERs for rats that began receiving phenytoin after the 25th day of avoidance training (which followed 31 days of appetitive training). The average avoidance rate over training days 21–25 (before the onset of drug treatment) was 78.5%. For training days 31–35, the rats now receiving phenytoin had a nearly identical 78.6% average rate of avoidance, $F(9, 45) = 1.03$, $p > 0.05$. Similarly, the average ER for training days 21–25 (0.590) was nearly identical with that for training days 31–35 [0.610; $F(9, 45) = 0.93$, $p > 0.05$].

Effects of Phenytoin on Avoidance Acquisition Without Prior Appetitive Experience

Figure 4 presents percent avoidances and efficiency ratios for rats treated with either phenytoin or water beginning 10 days before the training sessions began. Data from untreated control animals are also presented**.** The overall average avoidance rates for the last 5 days of training were 59.0 and 55.6% for the phenytoin treated and control animals. Avoidance data for water-treated and untreated control animals were again compared across training days 1–5 and 21–25, $F(1, 12) = 1.00$, $p > 0.05$; $F(1, 12) = 0.00$, $p > 0.05$. Animals treated with phenytoin from 10 days prior to training throughout avoidance training performed comparable to the pooled controls throughout the task. Neither of the avoidance performance comparisons yielded statistically significant differences, $F(1, 16) = 0.17$, $p > 0.05$; $F(1, 16) = 0.03$, $p > 0.05$. Similarly, the average ERs over the last 5 days of avoidance training were 0.44 and 0.38 for the phenytoin-treated and control rats, respectively. The water-treated and untreated controls ERs were statistically comparable across days 1–5 and 21–25, $F(1, 12) = 2.88$, $p > 0.05$; $F(1, 12) = 0.12$, $p > 0.05$. Phenytoin-treated animals, as compared to the pooled controls, demon-

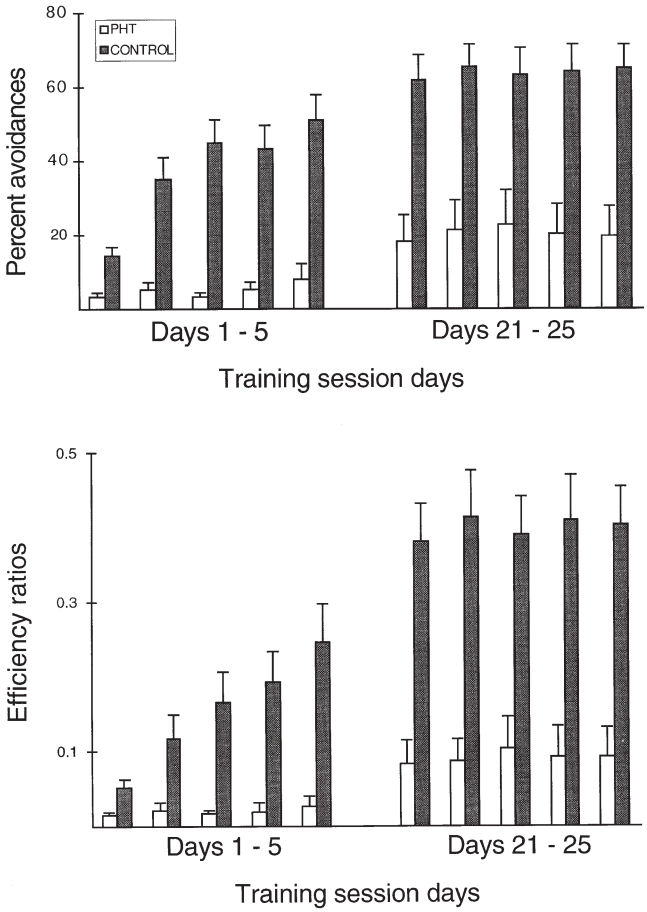

FIG. 2. Aversive context performance, as measured by percent avoidances and efficiency ratios, is illustrated for phenytoin-treated and control animals; data for water-treated and untreated controls are collapsed in these measures. Percent avoidance averages are presented for the first and last days of avoidance training. Phenytoin-treated animals demonstrate a slower acquisition of the avoidance response, and fail to avoid at control levels even during the last five days of training (20.5 vs. 64.1%, respectively). Efficiency ratios are presented for the first and last 5 days of avoidance training. Although both groups display relatively inefficient bar pressing behavior initially, phenytoin-treated animals fail to show the same level of improvement in efficiency that control animals demonstrate.

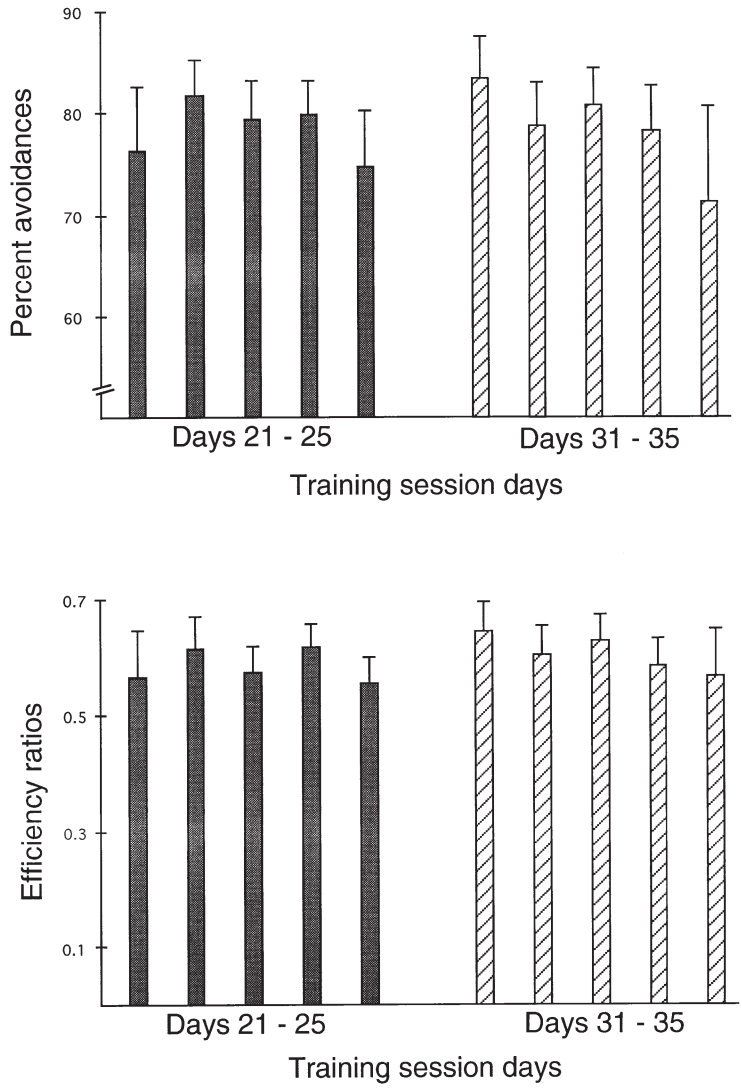

FIG. 3. Maintenance of avoidance performance, as measured by percent avoidances and efficiency ratios, is measured for animals initiating phenytoin treatment after the 25th day of avoidance training. Percent avoidances and efficiency ratios for days 21–25 (untreated) and 31–35 (phenytoin-treated) are unchanged by phenytoin-treatment.

strated similarly good performance, $F(1, 16) = 0.06, p > 0.05$; $F(1, 16) = 0.16, p > 0.05$.

DISCUSSION

Due to conflicting reports of the relative cognitive deficits in humans maintained on anticonvulsant drugs, there has developed a need for comprehensive evaluations of these drugs. The present experiments represent an effort to begin comparing the effects of various antiepileptic compounds in a single, well-defined experimental learning and memory paradigm. The results demonstrate that otherwise normal adult rats treated with phenytoin are severely impaired in their ability to acquire an avoidance response after prior appetitive training. This difficulty is not simply an impairment of learning in an aversive context, but rather appears to arise from difficulties associated with the transfer between contexts.

Effects of Phenytoin on Appetitive Performance

We report that rats beginning phenytoin treatment during appetitive training had slightly lower rates of reinforced bar presses at the end of training than did the control subjects (88.8 and 95.5%, respectively). This raised the possibility that the drug was reducing appetitive motivation. We noted, however, that the predrug performance levels of these rats were already somewhat lower than the control animals, and that acquisition was nearly identical to controls when drug treatment was initiated before appetitive training (96.9 and 95.5%, respectively). Importantly, the phenytoin-treated rats showed

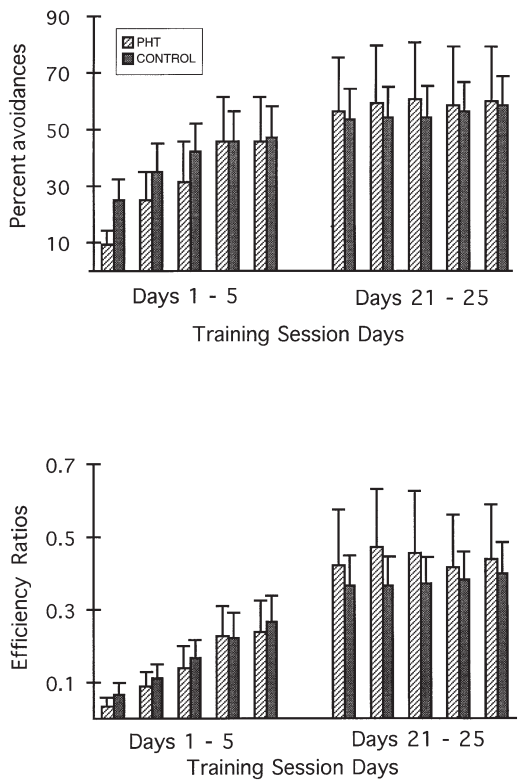

FIG. 4. Acquisition of avoidance performance, as measured by percent avoidances and efficiency ratios, is illustrated for phenytoin-treated and control animals. Phenytoin or water treatment was initiated 10 days prior to avoidance training (without prior appetitive experience). Avoidance acquisition data are combined for water-treated and untreated animals, for comparison with phenytoin-treated animals. Terminal avoidance rates and efficiency ratios are not statistically different for the groups.

no changes in percentages of reinforced bar presses due to the drug treatment, and their ERs improved over the 10 days of appetitive training after the initiation of drug treatment. This pattern of results is comparable to that found for the control animals. Thus, we think it is more likely that the lower terminal rates of reinforced bar presses in the rats in which drug treatment began during appetitive training reflect a small difference between the experimental groups that was not a direct result of the experimental manipulation.

Effects of Phenytoin on Avoidance Acquisition after Appetitive Training

At the conclusion of appetitive training, the rats were transferred to an aversive context in which an aversive stimulus could be actively avoided with a tone-signaled bar press. In the rats that began receiving phenytoin during appetitive training, avoidance acquisition was severely impaired. While the terminal avoidance rates in the control animals exceeded 60%, the phenytoin-treated rats avoided on only about 20% of the trials. The phenytoin-treated rats also displayed substantially lower ERs at the end of training relative to the control animals. Over the last 5 days of avoidance training, the phenytoin-treated rats were making in excess of 10 bar presses for each successful avoidance, whereas control animals were making only about 2.5 bar presses per avoidance. These differences in ERs were not due to large differences in the numbers of bar presses made by the drug-treated and control rats. Although the control animals did produce fewer bar presses than phenytoin-treated animals on average (557 and 691 bar presses per session, respectively, across the last 5 days of training), this difference is not large enough to fully account for the difference in efficiency ratios. Rather, the control animals were clearly distributing their responses more appropriately with respect to the tone signal than were the drug-treated rats.

Control Considerations

Sensory/motor slowing? Although we hypothesized that the failure of the phenytoin-treated rats to acquire the avoidance response after appetitive training was due to a difficulty with the transfer, several other possible explanations existed. For example, there have been reports in the human literature of longer latency brain stem auditory evoked potentials (13), and prolonged event-related potentials in human epileptics (18) and normal volunteers (1) who were being maintained on phenytoin. If the tone signal in the present experiment was processed more slowly in drug-treated rats, the animals could conceivably have learned the avoidance response but been too slow in producing it due to a simple sensory slowing. There have also been reports of motor slowing in humans receiving phenytoin [e.g., (2,17)]. Clearly, motor slowing could also delay an avoidance response so that it is coded as an escape.

Indifference or heightened reactivity to the aversive stimulus. Perhaps the phenytoin treatment affected sensory processing such that the shock was less motivating than in control rats. Alternatively, the phenytoin may have increased reactivity to the shock resulting in an increased freezing response. If phenytoin was producing sensory and/or motor slowing or raising or lowering reactivity to the shock, one would expect a decline in avoidance rate after the initiation of drug treatment in control animals that had completed the appetitive-to-aversive transfer. This was not the case in animals that began receiving on the 25th day of avoidance training; percent avoidances and ERs were unaffected over the ensuing 10 days of avoidance training.

Learning in an aversive context per se. At that point it remained possible that phenytoin's effects were specific to learning in an aversive context. The drug had been shown to have no effect on acquisition or retention of an appetitive response, and no effect on retention of the avoidance response, but it remained necessary to place drug-treated rats directly into avoidance learning (i.e., with no prior appetitive experience). The rats in this condition acquired the avoidance response as readily as controls. Thus, the failure of phenytoin-treated rats to learn the avoidance response after prior appetitive training must relate to difficulties associated with the transfer and not to any aversive context-specific effects of the drug.

CONCLUSIONS AND HYPOTHESES

Clearly, the drug-treated animals retain the ability to learn the relatively simple associations needed to perform in either the appetitive or aversive context alone. The learning deficit described here relates very specifically to the transfer from appetitive to aversive contexts. How phenytoin might produce this deficit is unclear, due to the uncertainty about what the explicit mechanism of action of the drug is; that is, the active site(s) of anticonvulsant and other actions of phenytoin remains controversial [e.g., for review, see (10)]. The forward-

acting nature of the learning deficit suggests a problem that resembles proactive interference, and the specificity of the deficit to the transfer suggests the possibility that the problem relates to an inability to shift strategy in the face of the altered contingencies. Although these possibilities are clearly speculative, they would both suggest that a site of action relevant to the transfer deficit involves frontal cortex, as frontal cortical lesions result in marked proactive interference [e.g., (28)], and deficits in performance on such measures as the Wisconsin Card Sorting Task (WCST), a task developed to assess the ability to develop and maintain appropriate problem-solving strategies across changing stimulus conditions (9,20). Although patients maintained on phenytoin have been reported to demonstrate impairments on such memory tasks as short-term memory scanning, word list learning, and story recall (4,42), measurements for proactive interference or deficits in executive function appear to be lacking from the literature. Interestingly, we have preliminary evidence that humans being maintained on carbamazepine are impaired in performing the WCST (8), but we do not have comparable data for phenytoin.

The goals of the present experiments were twofold. We wished to begin establishing the appetitive-to-aversive transfer paradigm as a model for evaluating the cognitive consequences of antiepileptic compounds, and to relate our findings to an extensive learning and memory literature so that we might begin to determine the relevant sites and neurochemical routes of action for antiepileptic drugs. Such a systematic approach may help to clarify discrepancies in previous findings, which compare only a limited number of medications or use different behavioral paradigms [e.g., (14,25,33)]. The results reported here suggest that this strategy may well prove fruitful. In addition, a systematic assessment of drug dose, plasma drug level, cerebrospinal fluid drug level, and behavior may yield pertinent information about the adverse effects and therapeutic efficacy of the drugs [see (22)]. Based on these early results, we can now extend our goals to encompass the ultimate one—identifying the drug (or class of drugs) that delivers maximal anticonvulsant protection with minimal negative cognitive deficits.

ACKNOWLEDGEMENTS

This work was supported by Indiana University funds 22-314-31, MH55548 (P.E.G.) and MH51178 (J.E.S.). The authors would like to acknowledge the generous gifts of time, guidance, and assistance provided by Dr. Mark Wisen.

REFERENCES

1. Akaho, R.: The effects of antiepileptic drugs on cognition in normal volunteers. Psychiatr. Clin. Neurosci. 50:61–69; 1996.
2. Aldenkamp, A. P.; Alpherts, W. C. L.; Diepman, L.; van 't Slot, B.; Overweg, J.; Vermeulen, J.: Cognitive side-effects of phenytoin compared with carbamazepine in patients with localization-related epilepsy. Epilepsy Res. 19:37–43; 1994.
3. Aman, M. G.; Werry, J. S.; Paxton, J. W.; Turbott, S. H.: Effects of phenytoin on cognitive-motor performance in children as a function of drug concentration, seizure type, and time of medication. Epilepsia 35:172–180; 1994.
4. Andrewes, D. G.; Bullen, J. G.; Tomlinson, L.; Elwes, R. D. C.; Reynolds, E. H.: A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. Epilepsia 27:128–134; 1986.
5. Banks, M. K.; Mohr, N. L.; Bernard, E. A.; Logue, S. F.; Steinmetz, J. E.; Garraghty, P. E.: A comparison of the effects of CPP and phenytoin on transfer from appetitive to aversive contexts in adult rats. Soc. Neurosci. Abstr. 21:204; 1995.
6. Banks, M. K.; Besheer, J.; Szypczak, J. R.; Goodpaster, L. L.; Steinmetz, J. E.; Garraghty, P. E.: A comparison of the effects of carbamazepine and phenytoin on transfer from appetitive to avoidance contexts in adult rats. Soc. Neurosci. Abstr. 22:2108; 1996.
7. Banks, M. K.; Churchill, J. D.; Besheer, J.; Voss, S. E.; Steinmetz, J. E.; Garraghty, P. E.: Phenytoin's antiepileptic actions apparently include a disruption of NMDA receptor function in the hippocampus. Am. Psychol. Soc. Abstr. (Biol. Basis Behav.) 9:37; 1997.
8. Banks, M. K.; Goodpaster, L. L.; Besheer, J.; Garraghty, P. E.: Effects of carbamazepine on learning and memory in animal and human subjects. Am. Psychol. Soc. 10:80; 1998.
9. Berg, E. A.: A simple objective test for measuring flexibility in thinking. J. Gen. Psychol. 39:15–22; 1948.
10. Browning, R. A.; Faingold, C. L.: Antiepileptic actions of hydantoins. In: Faingold, C. L.; Fromm, G. H., eds. Drugs for control of epilepsy: Actions on neuronal networks involved in seizure disorders. Boca Raton, FL: CRC Press; 1992:413–423.
11. Butlin, A. T.; Wolfendale, L.; Danta, G.: The effects of anticonvulsants on memory function in epileptic patients: preliminary findings. Clin. Exp. Neurol. 17:79–84; 1981.
12. Butlin, A. T.; Danta, G.; Cook, M. L.: Anticonvulsant effects on the memory performance of epileptics. Clin. Exp. Neurol. 20:27–35; 1984.
13. Chan, Y. W.; Woo, E.; Yu, Y. L.: Chronic effects of phenytoin on brain-stem auditory evoked potentials in man. EEG Clin. Neurophysiol. 77:119–126; 1990.
14. Chen, Y. J.; Kang, W. M.; So, W. C. M.: Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: A psychometric and neurophysiological study. Epilepsia 37:81–86; 1996.
15. Devinsky, O.: Cognitive and behavioral effects of antiepileptic drugs. Epilepsia 36(Suppl. 2):S46–S65; 1995.
16. Dodrill, C. B.: Cognitive and psychosocial effects of epilepsy on adults. In: Wyllie, E., ed. The treatment of epilepsy: Principles and and practices. Philadelphia: Lea & Febiger; 1993:1133–1140.
17. Dodrill, C. B.; Temkin, N. R.: Motor speed is a contaminating factor in evaluating the "cognitive" effects of phenytoin. Epilepsia 30:453–457; 1989.
18. Enoki, H.; Sanada, S.; Oka, E.; Ohtahara, S.: Effects of high-dose antiepileptic drugs on event-related potentials in epileptic children. Epilepsy Res. 25:59–64; 1996.
19. Gallassi, R.; Morreale, A.; Lorusso, S.; Procaccianti, G.; Lugaresi, E.; Baruzzi, A.: Carbamazepine and phenytoin: Comparison of cognitive effects in epileptic patients during monotherapy and withdrawal. Arch. Neurol. 45:892–894; 1988.
20. Grant, D. A.; Berg, E. A.: A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem. J. Exp. Psychol. 34:404–411; 1948.
21. Izquierdo, I.; Nasello, A. G.: Effects of cannabidiol and of diphenylhydantoin on the hippocampus and on learning. Psychopharmacologia 31:167–175; 1973.
22. Lammers, M. W.; Hekster, Y. A.; Keyser, A.; van Lier, H.; Meinardi, H.; Renier, W. O.: Neither dosage nor serum levels of antiepileptic drugs are predictive for efficacy and adverse effects. Pharm. World Sci. 17:201–206; 1995.
23. Logue, S. F.: An examination of the role of the hippocampus in the acquisition and timing of a signalled barpress in appetitive and aversive conditioning. Dissertation submitted to Indiana University, August, 1994.
24. Meador, K. J.: Cognitive side effects of antiepileptic drugs. Can. J. Neurol. Sci. 21(Suppl. 3):S12–S16; 1994.
25. Meador, K. J.; Loring, D. W.; Moore, E. E.; Thompson, W. O.;

Nichols, M. E.; Oberzan, R. E.; Durkin, M. W.; Gallagher, B. B.; King, D. W.: Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology 45:1494–1499; 1995.
26. Merritt, H. H.; Putnam, T. J.: Sodium diphenyl hydantoinate in treatment of convulsive disorders. JAMA 111:1068–1073; 1938.
27. Mohr, N. L.; Steinmetz, J. E.; Garraghty, P. E.: Effects of phenytoin on learned appetitive responses and the subsequent acquisition of escape and avoidance responses. Soc. Neurosci. Abstr. 20:1020; 1994.
28. Moscovitch, M.: Multiple dissociations of function in amnesia. In: Cermak, L. S., ed. Human memory and amnesia. Hillsdale, NJ: Erlbaum; 1982:337–370.
29. Poling, A.; Blakely, E.; White, W.; Picker, M.: Chronic effects of clonazepam, phenytoin, ethosuximide, and valproic acid on learning in pigeons as assayed by a repeated acquisition procedure. Pharmacol. Biochem. Behav. 24:1583–1586; 1986.
30. Pulliainen, V.; Jokelainen, M.: Effects of phenytoin and carbamazepine on cognitive functions in newly diagnosed epileptic patients. Acta Neurol. Scand. 89:81–86; 1994.
31. Pulliainen, V.; Jokelainen, M.: Comparing the cognitive effects of phenytoin and carbamazepine in long-term monotherapy: A two-year followup. Epilepsia 36:1195–1202; 1995.
32. Rall, T. W.; Schliefer, L. S.: Drugs effective in the therapy of the epilepsies. In: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. Goodman and Gilman's the pharmacological basis of therapeutics. New York: Pergamon Press; 1990:436–462.
33. Sabers, A.; Moller, A.; Dam, M.; Smed, A.; Arlien-Soborg, P.; Buchman, J.; Andersen, E. B.; Boesen, F.; Dam, A. M.; Lyon, B. B.; Pedersen, B.: Cognitive function and anticonvulsant therapy: Effect of monotherapy in epilepsy. Acta Neurol. Scand. 92:19–27; 1995.
34. Shalev, R. S.; Gross-Tsur, V.; Masur, D.: Cognition, behavior, and academic performance in children with epilepsy. Childhood Seizures 6:170–178; 1995.
35. Smith, D. B.; Mattson, R. H.; Cramer, J. A.; Collins, J. F.; Novelly, R. A.; Craft, B.; V.A.E.C.S.G.: Results of a nationwide veterans administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia 28(Suppl. 3):S50–S58; 1987.
36. Steinhausen, H. C.; Rauss-Mason, C.: Epilepsy and anticonvulsive drugs. In: Rutter, M.; Casaer, P., eds. Biological risk factors for psychosocial disorder. Cambridge: Cambridge University Press; 1991:311–339.
37. Steinmetz, J. E.; Logue, S. F.; Miller, D. P.: Using signalled barpressing tasks to study the neural substrates of appetitive and aversive learning in rats: Behavioral manipulations and cerebellar lesions. Behav. Neurosci. 107:941–954; 1993.
38. Thompson, P.; Huppert, F. A.; Trimble, M.: Phenytoin and cognitive function: Effects on normal volunteers and implications for epilepsy. Br. J. Clin. Psychol. 20:155–162; 1981.
39. Thompson, P. J.; Trimble, M. R.: Anticonvulsant drugs and cognitive functions. Epilepsia 23:531–544; 1982.
40. Tonnby, B.; Nilsson, H. L.; Aldenkamp, A. P.; Alpherts, W. C. J.; Blennow, G.; Elmqvist, D.; Heijbel, J.; Sandstedt, P.; Wahlander, L.; Wosse, E.: Withdrawal of antiepileptic medication in children: Correlation of cognitive function and plasma concentration—The multicentre 'Holmfrid' study. Epilepsy Res. 19:141–152; 1994.
41. Trimble, M.: The effect of anti-convulsant drugs on cognitive abilities. Pharmacol. Ther. 4:677–685; 1979.
42. Trimble, M. R.: Anticonvulsant drugs and cognitive function: A review of the literature. Epilepsia 28(Suppl. 3): S37–S45; 1987.
43. Tsai, L. S.: Interrelated effects of Dilantin and electroconvulsive shock upon onetrial revesal learning in white rats. Psychol. Rep. 61:992–994; 1987.
44. Tuunainen, A.; Hurskainen, H.; Nousiainen, U.; Pilke, A.; Riekkiinen, P.: Short-term withdrawal of antiepileptic medication: Effects on attention and memory. Acta Neurol. Scand. 92:198–205; 1995.
45. Vermeulen, J.; Aldencamp, A. P.: Cognitive side-effects chronic antiepileptic drug treatment: A review of 25 years of research. Epilepsy Res. 22:65–95; 1995.