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Phenytoin and Phenobarbital: A Comparison of Their State-Dependent Effects

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KUMAR, K. B., S. RAMALINGAM AND K. S. KARANTH. *Phenytoin and phenobarbital: A comparison of their state-dependent effects.* PHARMACOL BIOCHEM BEHAV 47(4) 951–956, 1994.—Two commonly used antiepileptic drugs, phenytoin sodium and phenobarbital sodium, were investigated for state-dependency effects at different doses. Male Wistar strain rats trained to a criterion in an inhibitory avoidance task and a food-motivated T-maze task under varying drug and nondrug states were subjected to retention tests 24 and 48 h, respectively, following acquisition. The treatment instituted at the time of retrieval was either the same as, or different from, that used during training. The results indicated that phenytoin produced state-dependency effects at test doses of 20, 40, and 60 mg/kg in the avoidance task and at test dose of 20 mg/kg in the T-maze task experiments. These state-specific effects were comparable to those of phenobarbital sodium (5 and 10 mg/kg). The reinstitution of the drug state in an additional test session produced approximately equal and significant recovery of conditioned responses in the T-maze paradigm both in phenytoin and phenobarbital groups. These results demonstrate, for the first time, the ability of phenytoin to produce state-dependency effects in a pattern similar to that observed with a widely studied compound such as phenobarbital. Overall, the data provide no support for the view that the degree of discriminability of a drug is an indicator of potential state-dependency effects and is restricted only to the dosage high enough to produce noticeable intoxication.

Drug discriminability State-dependency Phenytoin Phenobarbital Inhibitory avoidance T-maze

THE term state-dependency (StD) describes the observation that a behavior learned in a particular state becomes most easily retrievable only if the state present during learning is restored (17). Drug discriminability (DD) refers to those properties of a drug that allow discriminative control to develop guiding a behavioral choice (26). Measurements of the degree of discriminability of drugs are believed to indicate their capacity to produce state-dependent learning. For example, Eich (13) and Overton (26) suggested that a drug showing a high degree of discriminability is more likely to produce state-dependent effects than a drug showing a low degree of discriminability. But, unfortunately, there is no unanimity with regard to degree of discriminability of a drug as a measure of the strength of the StD effects. Some investigators have proposed that the DD and StD are one and the same phenomenon reflecting the same underlying properties of drugs (2,27) and others have argued that the processes underlying DD and StD may differ (6,10).

State-dependency-like effects have been reported for a number of psychoactive drugs (11,15,30). Among the antiepileptics, phenobarbital sodium is reported to have high DD and to produce StD (26,27). The StD features of phenytoin sodium and other commonly used antiepileptic drugs, however, have not been as well examined. Studying the DD of various psychoactive drugs in a shock–escape procedure, Overton (26) reported phenytoin sodium to be a drug having low discriminability, and linking DD with StD predicted this drug to be less likely to produce StD. In contrast, few other studies have reported the ability of phenytoin sodium to readily act as a behavioral discriminative stimulus in operant tasks (20,21,29). In the backdrop of these varying observations of the effects of phenytoin sodium in DD designs, the present study was planned to compare the StD features of phenytoin sodium, a drug that has not been previously studied using StD experimental designs, with those of phenobarbital sodium, a drug with high discriminability and established StD effect.

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Two experiments were conducted. Experiment 1 studied the StD effects of different doses of both phenytoin sodium and phenobarbital sodium in an inhibitory avoidance task. Experiment 2 further examined the low-dose effects of both drugs in an appetitive T-maze task.

EXPERIMENT 1: INHIBITORY AVOIDANCE TASK

The animals trained under drug or no-drug conditions in an inhibitory avoidance task were subjected to retention testing 24 h following acquisition. The treatment instituted at the time of retrieval was either the same as or different from that used during acquisition.

METHOD

Subjects

Inbred male albino rats of a Wistar strain weighing 220–250 g were used. The age of the animals ranged between 70 and 90 days and they were maintained under 12 L : 12 D cycle (lights on 0600–1800 h) with food and water ad lib. Animals were individually housed and handled for approximately 20 min per day, 3 days prior to the experiments. All procedures were carried out in the early part of the dark cycle (between 1830 and 2330 h).

Drugs

Three doses of phenobarbital sodium (2.5, 5, and 10 mg/kg) and phenytoin sodium (20, 40, and 60 mg/kg) were used in these experiments. Phenobarbital sodium was dissolved in distilled water. Phenytoin sodium was dissolved in propylene glycol to yield the desired concentration in 0.2 ml of the solvent. Both the drugs were injected IP 1 h before the experiments. The injection–test interval was based on the assumption that "discriminable drug effects would have the same time course as did the visible drug effects on motor coordination" (26). The drug-induced impairment of motor coordination was determined by the inclined plane and traction tests (data not shown) as described by Turner (31). Doses of the two drugs are expressed in terms of the forms described above.

Procedure

The inhibitory avoidance test apparatus was designed according to the description by Bures et al. (4). In brief, the apparatus consisted of two compartments (50 × 50 and 15 × 15 cm) with a 6 × 6 cm transparent Plexiglas sliding door connecting the two compartments. The small compartment was provided with an electrifiable floor grid connected to a shock generator (Hugo Sachs Electronik, Germany). A light source of 100-W bulb was located 150 cm above the large compartment. A 3-min habituation period was allowed 30 min before subjecting the animals to the learning trials. On every trial a subject was placed in the bright compartment with its nose facing away from the dark compartment. When an animal entered the dark compartment with all limbs inside, the door was closed and a 2-s duration foot shock of 0.8 mA was delivered immediately. At the end of the shock delivery, the door was opened and on exit the animal was removed and returned to its home cage. One minute later, the animal was reintroduced into the chamber and observed for 180 s. Complete bodily entry into the dark compartment within this time period resulted in shock delivery as before; no entry was considered an indicator of learning (3). Total number of trials required by each animal to meet this criterion were recorded. Twenty-four hours following the learning trials, the animals were subjected to retention tests. One hour before the retention trial, the animals were treated either with drug or vehicle as dictated by the group concerned. Animals were placed in the bright compartment as described above and were observed for a period of 180 s. Entry or no entry into the dark compartment within this period was noted for each animal as the index of retention. The experimenter performing the recordings was blind to the treatment instituted. Three groups (n = 8) were employed for each dose of both drugs. Group 1 received drug during learning and on retention (D–D); group 2 received drug during learning and vehicle on retention (D–N); and group 3 received vehicle during learning and drug on retention (N–D). In addition, one more control group (n = 8) for each drug was employed that received vehicle both during learning and on retention (N–N).

Data Analysis

One-way analysis of variance (ANOVA) was performed for comparisons of data pertaining to the learning trials involving multiple groups. When statistical significance was indicated by ANOVA (i.e., $p < 0.05$), individual mean comparisons were made using Duncan's post hoc test. A chi-square test was applied to the analysis of retention test results of animals categorized as having exhibited retrieval or no retrieval.

RESULTS

The effect of various doses of both the drugs on the inhibitory avoidance learning is shown in Table 1. Because there was no significant difference between the two vehicle-treated control groups, the observations were combined for statistical purposes. Similarly, the D–D and D–N groups were also combined for assessing the effect of drug on acquisition. A significant interaction between the various doses of phenobarbital sodium, $F(3, 60) = 3.83$, $p < 0.05$, and phenytoin sodium, $F(3, 60) = 2.96$, $p < 0.05$, was observed in the rate of learn-

TABLE 1

MEAN ± SEM NUMBER OF TRIALS REQUIRED TO MEET THE LEARNING CRITERION IN INHIBITORY AVOIDANCE TASK

Phenobarbital (n = 16)			Phenytoin (n = 16)			Control Vehicle (n = 16)
2.5 mg	5 mg	10 mg	20 mg	40 mg	60 mg	
1.19 ± 0.09	1.44 ± 0.13	1.75 ± 0.11	1.19 ± 0.10	1.69 ± 0.12	1.44 ± 0.13	1.50 ± 0.13

No significant differences between control and any of the drug-treated groups at any doses in individual mean values (Duncan's post hoc test).

TABLE 2
RETRIEVAL PERFORMANCE IN INHIBITORY AVOIDANCE TASK

Group	Phenobarbital (n = 8)			Phenytoin (n = 8)			Control Vehicle (n = 16)
	2.5 mg	5 mg	10 mg	20 mg	40 mg	60 mg	
D-D	12.5	12.5	12.5	25.0	12.5	12.5	
D-N	00.0	87.5*	75.0*	87.5*	100.0*	100.0*	
N-D	00.0	12.5	00.0	25.0	12.5	00.0	
N-N							12.5

Values are given as the percentage of animals that entered the dark compartment.
*Significantly differs from the control ($p < 0.01$).

ing. Subsequent individual mean comparisons did not show significant differences between vehicle-treated control and any of the drug-treated groups at any dose.

The retention test results are shown in Table 2. Compared to the control (N-N) group, the retrieval performance of the D-N group of both the drugs was significantly affected ($p < 0.01$) at all doses, except for the group that received the lowest dose (2.5 mg/kg) of phenobarbital sodium. No performance deficit was noted for either of the D-D and N-D groups.

DISCUSSION

A significant decrease in the transfer of avoidance performance was seen for the animals tested in the drug-free state as indicated by increased percent entry into the dark compartment during testing when acquisition had occurred in a drug state. This StD effect was noticed for both the drugs at all doses used except for the lowest dose of phenobarbital. Neither of the other two groups, namely D-D and N-D groups, showed any transfer deficit. Lack of transfer deficit for the lowest dose of phenobarbital in the present study is consistent with the findings of Panda (unpublished observations) using radial-maze and one-way active avoidance tasks. Together, these findings indicate that 2.5 mg/kg of phenobarbital is a subthreshold dose for demonstrating StD phenomenon. The absence of a retrieval performance deficit in the N-D groups for both the drugs is consistent with the view that StD retrieval deficits are often asymmetrical (27). A reasonable presumption from all these experimental data would be that phenytoin sodium, despite having a low DD index as previously assessed in a T-maze with shock-escape systems (26), produces StD to a degree that is comparable to a drug with a high DD index. Further, it is interesting to note that both the drugs that were used in the present study have produced this effect at doses far lower than those used in an earlier drug discrimination study (26). Thus, this finding does not substantiate the earlier assumption (13,17) that the deleterious effect (retrieval dissociation) of an anticonvulsant agent is related to the dose intensity. However, note that the doses of phenytoin sodium used in this study are high relative to those at which discriminative properties of this drug have been reported (5-20 mg/kg) (20,21,29).

EXPERIMENT 2: APPETITIVE T-MAZE TASK

Inhibitory avoidance as a paradigm involves delivering foot shocks to a subject as it enters a darkened compartment. This paradigm may therefore suffer from the disadvantage that the animal might develop a "fear complex" as a result of the shock it receives during learning trials (1). The effects of emotional states on memory retrieval in the context of state-dependent learning have been considered as substantial as those induced by other contextual cues (27), and may confound the "characteristic" pharmacological actions of the drugs (26). Most of the earlier studies (18,19,22,26) used T-maze, shock-escape systems to study the degree of discriminability of the drugs used in the present study. To avoid possible confounding by an emotional state, we investigated the StD effects of both phenytoin and phenobarbital sodium in a punishment-free paradigm, namely the appetitive T-maze, in this experiment. We also examined whether retrieval deficits seen in the nondrugged retention condition among the D-N animals could be overcome if the learning drug state were restored subsequent to the first retention test.

METHOD

Subjects

Rats of the same strain and age as those described in Experiment 1 were used in this study. Animals were maintained on a schedule of food deprivation (up to 90% of baseline body weight) with free access to water. All animals were trained and tested during their dark cycle as in previous experiments.

Drugs

Only the lowest doses of phenobarbital sodium (5 mg/kg) and phenytoin sodium (20 mg/kg) with which StD effects were seen in the previous experiment were used in these experiments. Drugs were dissolved and administered 1 h before the experiments on all days, as described earlier.

Procedure

The T-maze task employed in this study was essentially a simultaneous brightness discrimination learning under appetitive motivation (4). The correct arm of the T-maze was illuminated, whereas the incorrect arm was dark. The T-maze apparatus used was similar to the one described by Overton (26), with the following modifications. A 100-W spotlight was placed 100 cm above the start point rather than at the choice point. A regular 15-W bulb was hung on either side of the horizontal limb of the "T." These light bulbs could be switched on/off independent of each other. Care was taken to prevent the light from diffusing to the other arm when the bulb in one arm was switched on. Animals (denied food for 6 h prior to the learning trials) were dropped from a height of about 10 cm onto the floor of the start compartment facing the choice

TABLE 3

MEAN ± SEM NUMBER OF TRIALS TO MEET THE CRITERION IN AN APPETITIVE TASK

Phenobarbital (5 mg, n = 16)	Phenytoin (20 mg, n = 16)	Control Vehicle (n = 16)
88.0 ± 4.89	86.7 ± 5.60	90.0 ± 4.45

No significant difference among the groups (ANOVA).

area. At the same time, the light above the start point was turned on. The light on the side where the food pellets (Lipton India Ltd., about 200 mg) were available was already on. The alley in which the food was to be found was varied on each trial according to a prerandomized sequence. In each trial, animals were allowed to make one entry into either of the two goal boxes. A correct choice consisted of the animal entering the illuminated arm where food was available. Irrespective of the choice, the animal was required to return to the choice area before being returned to the home cage. To prevent the recognition of a baited alley by the smell of food, the maze was saturated by food odor (4). Twenty daily trials were given per animal with an intertrial interval of 1 min. Training trials continued until the animal made at least 90% correct choices on 2 consecutive days. At the end of each daily training session, a fixed quantity of food was delivered in the home cage after adjusting to the total weight of food an individual animal had already consumed during the training trials. The first retention test of 10 trials was carried out 48 h after an animal had attained the training criterion. The second test of 10 trials occurred 1 h after the last trial of the first retention test. Testing occurred under various drugged and nondrugged states depending on group assignment. Test trials were conducted in the same manner as for the training trials. The number of correct choices made by each animal was recorded, and group data are presented as the mean correct choice. Four groups (n = 8) of animals for each drug were employed. Group 1 received drug during training and vehicle on retention I and II (D-N-N); group 2 received drug during training and retention II, vehicle on retention I (D-N-D); group 3 received vehicle during training and retention I, drug on retention II (N-N-D); group 4 received vehicle on all occasions (N-N-N).

Data Analysis

One-way ANOVA was performed comparing mean number of trials needed to meet criterion across groups. The results of the retention tests were analyzed using Student's t-test for independent and nonindependent groups.

RESULTS

Because there was no significant difference between the two vehicle-treated control groups, group 3 (N-N-D) and 4 (N-N-N) observations were combined for computation. Similarly, group 1 (D-N-N) and 2 (D-N-D) observations were also combined under each drug to assess the effects of drug on acquisition and retrieval status at retention test I. The number of trials required to meet the criterion during the initial training phase for the different groups is given in Table 3. No significant difference was seen among the groups in the rate of learning, $F(2, 45) = 0.4967, p > 0.05$. On retention test I, a decreased number of correct choices in the D-N-N and D-N-D groups (Table 4) was seen with both drugs. This decrement in the retrieval performance was significantly less for the phenobarbital ($p < 0.001$) and phenytoin sodium ($p < 0.001$) groups compared to their respective vehicle-treated controls (i.e., N-N-D and N-N-N observations combined group). This performance decrement in nondrug state indicated a failure of learning transfer from drug to the nondrug state. However, at retention test II, when the drug state was restored (D-N-D), the retrieval performance increased significantly in both the phenobarbital ($p < 0.01$) and the phenytoin sodium ($p < 0.01$) groups compared to the performance under undrugged state. In the nonrestored (D-N-N) group, on the other hand, the retrieval deficits persisted approximately to the same degree as that found in retention test I for both the drugs. A complete transfer was observed in the remaining two groups (i.e., N-N-D and N-N-N) at retention test I and performance improved further during retention test II in both these groups (N-N-D group: $p < 0.05$; N-N-N group: $p < 0.01$).

DISCUSSION

As was observed in Experiment 1, a significant transfer deficit was detected under drug-free conditions for the appetitive T-maze task learned under drug condition. Both phenobarbital and phenytoin groups evinced approximately equal and significant decrease in number of conditioned responses at retention test I. However, at retention test II, when drug state was reinstituted (as was the case with the D-N-D group), the number of correct choices improved significantly compared to the performance in the nondrug state. This was true for both phenobarbital and phenytoin states. These data therefore add to previous evidence (Experiment 1) demon-

TABLE 4

MEAN ± SEM NUMBER OF CORRECT CHOICES IN APPETITIVE TASK DURING RETENTION TESTS

	Phenobarbital (5 mg)		Phenytoin (20 mg)		Vehicle	
Group	Retention I	Retention II	Retention I	Retention II	Retention I	Retention II
N-N-D (n = 8)	8.20 ± 0.29	9.40 ± 0.25*	8.10 ± 0.35	9.50 ± 0.22*		
D-N-N (n = 8)	3.20 ± 0.38†	3.20 ± 0.28	3.12 ± 0.23†	3.62 ± 0.26		
D-N-D (n = 8)	3.60 ± 0.51†	8.60 ± 0.25‡	3.25 ± 0.28†	8.25 ± 0.33§		
N-N-N (n = 16)					8.00 ± 0.26	9.30 ± 0.33‡

*‡§Significantly different from the values given at retention test I for respective group: *$p < 0.05$, ‡$p < 0.01$, §$p < 0.001$ (Student's t-test for nonindependent group).

†Significantly different from vehicle-treated control group at retention test I, $p < 0.001$ (Student's t-test for independent group).

strating that phenytoin sodium exerts stimulus state similar to that of phenobarbital sodium in StD designs. The lack of performance deficits in the N-N-D group during retention test II, when the drug was instituted, further supports the asymmetrical nature of StD retrieval deficits.

GENERAL DISCUSSION

Although in recent decades the state-dependent learning and drug discrimination paradigms have attracted wide interest in the field of behavioral pharmacology, these phenomena are yet to be established as a robust feature of a defined drug state either in human or infrahuman studies (12,14,24,32,33). Järbe (17) recently reviewed all the relevant data bearing on StD and DD paradigms, and concluded that state-dependent learning is not strong, is subject to development of tolerance, and vanishes with overtraining. Similarly, the generalization of data from drug discrimination studies has been daunted by several intrinsic problems. The mechanisms by which drugs achieve behavioral control in drug discrimination paradigms may depend on a variety of interceptive and exteroceptive stimuli (28), and these stimulus properties may be subject to various experimental manipulations (23). With respect to the present study, a long-standing controversy as to whether StD and discriminative drug effects reflect the same phenomenon or whether the processes underlying each of these are different (see the Introduction) is important. The StD effect has been predicted to occur or not to occur with certain psychoactive drugs based on the results in a drug discrimination paradigm. This prediction rested on the assumption that StD and DD are closely related and hence reflect the same properties of drugs (26,27).

Given the above conjecture that StD and DD reflect the same process of a drug, the state-specific effects may be expected to occur among anticonvulsants when a highly discriminable drug (e.g., phenobarbital sodium) is used rather than when a weakly discriminable drug (e.g., phenytoin sodium). The results of the present study, however, do not support such an assumption. Phenytoin, a drug reported as only weakly discriminable (25,26) and thus predicted to exert no deleterious effect on memory, produced retrieval amnesia both in an inhibitory avoidance and in a food-motivated T-maze task of the same magnitude as the purportedly highly discriminable drug phenobarbital. Thus, the assumption that the processes underlying StD and DD are one and the same is probably not true. Colpaert (6) makes a clear distinction between StD and DD paradigms, suggesting that these two phenomena are qualitatively different and independent of one another. The finding that cocaine (despite having a high degree of discriminability) failed to produce StD effects in an otherwise similar paradigm (9) supported this view point. Further, it has been observed that the level of discriminability of a particular drug may differ based on the procedural task used to determine the discriminability (16). The observed discordant effects of phenytoin sodium in operant and aversive task DD procedures (see the Introduction) also suggest the same. Therefore, the degree of discriminability of a drug may not be an unerring pointer of its capacity to produce StD.

Further it has been stated (13,17) that StD operates at the higher dose ranges (behaviorally toxic doses) of a drug and consequently StD can be appreciated in clinical and experimental conditions where high drug doses are likely to be used. But in this study, StD effects were observed even with rather low drug doses. This finding is in agreement with other studies (7,8) that have investigated the effect of low doses of a drug and demonstrated robust and quantifiable transfer deficits. Together, these findings indicate that the dose may not be a limiting factor of StD.

The present observation that responses acquired in a drug state remained unretrievable in the nondrug state (despite an additional test session) and then showed a rapid recovery following a restoration of the drug state indicated the robust nature of StD effect for both drugs. The fact that the restoration could be achieved with only a single injection of the drugs at the same doses that were used at the time of acquisition rules out any possibility of development of tolerance (5) in animals, due to repeated administration of drug during acquisition and its association with the observed StD effects.

In summary, the results of this study indicate that phenytoin sodium (a drug that had earlier been shown to have a low discriminability and thus predicted to have no state-specific effects) produced state-dependent retrieval amnesia to a degree that is comparable with a drug considered to have higher drug discriminability. This finding, therefore, does not substantiate the assumption that StD and DD reflect the same underlying properties of a drug. The StD effects were noticed for both the drugs at doses far lower than the dose known to produce drug intoxication, indicating that dose may not be a limiting factor of StD. Greater caution may be warranted in predicting the safety profile of these drugs used during therapy. Future studies will have to be conducted in volunteers to assess the relevance of these findings to humans.

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