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The effects of felbamate on appetitive and aversive instrumental learning in adult rats

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ABSTRACT

Antiepileptic medications are the frontline treatment for seizure conditions but are not without cognitive side effects. Previously, our laboratory reported learning deficits in phenytoin-, carbamazepine-, and valproate-treated rats. In the present experiment, the effects of felbamate (FBM) have been compared to water-treated controls (controls) using the same instrumental training tasks employed here. Rats treated with FBM displayed a deficit in acquiring a tone-signaled avoidance response, relative to controls, but this was true only if they had no prior appetitive experience. Terminal avoidance behavior was equivalent to healthy controls. In contrast, the FBM-treated rats showed enhanced acquisition of the avoidance response relative to controls when given the benefit of prior experience in the appetitive condition. Relative to animals treated with phenytoin, carbamazepine, or valproate, FBM-treated rats showed the lowest overall pattern of deficits using these instrumental learning tasks. While FBM treatment has been severely restricted because of rather low risks of serious medical side effects, we suggest that the risks are not substantially higher than those shown to exist for phenytoin, carbamazepine, or valproate. As psychologists, we further suggest that negative cognitive deficits associated with these various drugs, along with their quality-of-life costs, are of relevance in the design of treatment strategies for individuals with seizure disorders.

1. Introduction

Antiepileptic drugs (AEDs) are the frontline treatment for epilepsy but are not without cognitive side effects [e.g., 1,2]. Many studies have reported cognitive deficits in human patients treated with AEDs [e.g., 3–9]; for reviews, see [10–12]. Performance deficits have also been observed in animals treated with AEDs [e.g., 13–15], though other studies performed in animals have failed to detect cognitive deficits associated with AED treatment [16,17]. Previously, our laboratory has reported different types of behavioral deficits in adult rats treated with the AEDs phenytoin [18], carbamazepine [19], and valproate [20]. It was shown that phenytoin, and to a lesser degree, carbamazepine, both frontline AEDs, blocked the acquisition of an avoidance response in the second part of an instrumental appetitive-to-aversive transfer conditioning task [18,19]. More recently, we have shown that valproate produces a different pattern of deficits, impairing the acquisition of an avoidance response in the absence of prior appetitive training, but having no effect on avoidance learning in rats transferred from appetitive training [20].

In the present study, we have employed this same within-subject, tone-signaled bar press task in which rats are tested in both appetitive and aversive contexts. The task employed is complex and multicontextual. There are multiple rules in the aversive context that must be learned through conditioning. In the aversive context, rats must learn to both press the lever after the tone and not to press the lever during the intertrial period. 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 [21,22]. We have used this behavioral paradigm to evaluate the effects of phenytoin, carbamazepine, and valproate in adult rats [18–20,23], rats exposed to phenytoin in utero [24], rats with lesions of the basal nucleus of Meynart [25], ovariectomized female rats with or without estradiol replacement [26], and rats undergoing chronic restraint [27,28].

In the current study, we have extended our assessment of the cognitive side effects of AEDs to felbamate (FBM). Like phenytoin and carbamazepine, FBM and valproate have broad spectrum anticonvulsant activity [29], but unlike those compounds, FBM and valproate are also prescribed to be effective in treating absence and myoclonic seizures [e.g., 30,31]. Thus, the present study continues our effort to systematically evaluate the effects of various antiseizure medications using the same instrumental learning procedures, affording the

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opportunity for direct side-to-side comparisons of the various medications [see 12].

2. Materials and methods

2.1. Subjects

Data are reported for 55 adult Sprague–Dawley rats that were bred in the care facility in the Psychology Building at Indiana University. All experimental procedures were approved by the Indiana University Animal Care and Use Committee with policies derived from the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). Because previous publications have employed only female rats [18–20], only females were tested for the present report so that outcomes could be compared across experiments. Thus, we emphasize that generalizability to males for the present and previous results may be limited. Because subjects in the present experiments were tested over 25–56 days involving multiple estrus cycles, these cycles were not monitored, as any within-subject variability that might arise from hormonal fluctuations would be expected to be averaged out over the extended training period.

The animals were placed on food restriction beginning 10 days prior to initial training. When target weights were achieved, they were maintained at 85% free-feeding body weight throughout the study. If the animals were to undergo appetitive training, the 45-mg food pellets used as reinforcers (Bio-Serve, Frenchtown, NJ) were introduced to the animals in their home cages at least 2 days prior to the beginning of training.

Training was conducted in an operant testing box (Lafayette) placed in a lighted (10-W utility bulb) sound-attenuating chamber equipped with a center-mounted speaker to deliver a 2 kHz (at 90 dB sound pressure level (SPL)) tone.

2.2. Back wire implantation

A simple surgical procedure was used to implant two back wires that served as the connection points for the active lead for the delivery of electric shock during aversive training. For this procedure, anesthesia was induced with a mixture of ketamine and xylazine (60 and 6 mg/kg, respectively, IM). As the procedure could be accomplished in a matter of minutes, supplemental doses were rarely required, but given as needed.

Two double-loop 30 gauge surgical wires separated by approximately 1 cm apart were implanted subcutaneously between the scapulae of each animal. Animals also received 0.2 cm^3 Dopram (IM) and antibiotic ointment on the area of the wires. The entire procedure took approximately 15 min per subject.

2.3. Drug administration

Felbamate or water was administered as stated in the detailed methods for each experimental condition. Felbamate-treated animals received two daily doses totaling 3000 mg of the drug per day. One of the dosages was delivered 2 h before training. We have shown this regimen to produce plasma levels within or slightly below the human therapeutic range during the training period [32; and unpublished plasma assay data].

2.4. Appetitive training

All training sessions were separated by 24 h. For appetitive training, the animals were first shaped to bar-press for food reinforcement. When the animal achieved 100 reinforced responses within 30 min on a continuous reinforcement schedule, they were shifted to a fixed-ratio reinforcement schedule, with one reinforce delivered after four responses. This served to render the behavior more resistant to extinction. Under these conditions, two consecutive days with the animal performing 400 bar presses (i.e., 100 reinforcements) within 30 min were required before tone training was initiated.

During the tone-signaled sessions, the tone served as a positive discriminative stimulus. Reinforcement was delivered only for bar presses during the 3-s tone period.

One session consisted of 100 tones, each lasting 3 s or until the food pellet was delivered. A reinforced response was followed by a 15-s intertrial interval (ITI) and a randomly determined 1–8-s pretone period. Bar presses during the pretone period restarted the period, and the trial was delayed until no bar presses occurred during the randomly determined pretone period. Appetitive tone training continued for a total of 31 days.

2.5. Aversive training

At the conclusion of appetitive training, animals were transferred to the active avoidance task. Aversive training began with the animals receiving a shock that could be terminated by a bar press. The shock intensity was generally maintained at 0.7 mA, and never exceeded 1.0 mA. For the single session of aversive shaping, shock pulses were presented continuously until the bar was pressed. Animals were required to press the bar prior to the onset of the fifth shock pulse at least 15–20 times consecutively.

Tone training, using the same 2 kHz tone used for appetitive training, commenced on the following day. For aversive training, the tone served as a discriminative stimulus for an impending foot shock. A bar press during the first 3 s of tone presentation permitted the animal to avoid the shock. If an avoidance response was not produced, the tone and the shock pulsed continued for another 3 s. A bar press during this latter 3 s interval terminated the shock and the tone (i.e., an escape response). The shocks were delivered as a series of four 250-millisecond pulses separated by 500-millisecond periods.

Continuous shock pulses were delivered if the animal maintained a bar press for 5 s. This punished the animals for adopting a strategy of holding the bar down for excessive amounts of time (thereby avoiding the shock). Tone trials were separated by 8–12-s ITIs and a variable 2–6-s pretone period. A bar press during the ITI or pretone period reset the pretone period and delayed the initiation of the next trial. One session consisted of 300 tone trials. Aversive training continued for 25 days.

2.6. Experimental conditions

2.6.1. Effects of FBM on appetitive-to-aversive transfer

Eight rats began receiving FBM at the conclusion of the 21st day of appetitive training. For 6 additional animals, water treatment was initiated. Appetitive tone training continued for 10 days to assess any possible effect of the drug and/or gavage procedure on the acquired response.

Behavioral testing began 2 h after drug or water administration which continued daily throughout the remaining appetitive and total number of avoidance training sessions. A third cohort of rats served as untreated controls ($N = 12$), receiving no gavage treatment throughout the appetitive and avoidance training.

2.6.2. Effects of FBM on avoidance acquisition without prior appetitive experience

Another group of animals began avoidance training 10 days after the initiation of treatment with FBM ($N = 8$) or water ($N = 10$). Again, drug or water treatment continued throughout the 25 days of avoidance training. Additional animals ($N = 11$) underwent aversive training with neither drug nor water delivered via gavage. As above, one session of aversive shaping was followed by the 25 days of tone-signaled avoidance training. All parameters in the aversive context remained as