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Effects of antiepileptic drugs on attention as assessed by a five-choice serial reaction time task in rats

Harlan E. Shannon *, Patrick L. Love

Lilly Research Laboratories, Eli Lilly & Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

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Abstract

Patients with epilepsy can have impaired cognitive abilities. Antiepileptic drugs (AEDs) may contribute to the cognitive deficits observed in patients with epilepsy, and have been shown to induce cognitive impairments in healthy individuals. However, there are few systematic data on the effects of AEDs on specific cognitive domains. We have previously evaluated a number of AEDs with respect to their effects on working memory. The purpose of the present study was to evaluate the effects of AEDs on attention as measured by five-choice serial reaction time behavior in nonepileptic rats. The GABA-related AEDs triazolam, phenobarbital, and chlordiazepoxide significantly disrupted performance by increasing errors of omission, whereas tiagabine, valproate, and gabapentin did not. The sodium channel blocker carbamazepine increased errors of omission at relatively high doses, whereas the sodium channel blockers phenytoin, topiramate, and lamotrigine were without significant effect. Levetiracetam had no effect on attention. The disruptions produced by triazolam, phenobarbital, chlordiazepoxide, and carbamazepine were similar in magnitude to the effects of the muscarinic cholinergic receptor antagonist scopolamine. The present results indicate that AEDs can disrupt attention, but there are differences among AEDs in the magnitude of the disruption in nonepileptic rats, with drugs that enhance GABA receptor function producing the most consistent disruption of attention.
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1. Introduction

Patients with epilepsy may have impaired cognitive abilities and it may be that antiepileptic drug (AED) therapy may contribute to this impairment (see, e.g., [1–4]). In patients with epilepsy and/or normal volunteers, carbamazepine, phenytoin, and valproate have been reported to adversely affect cognition to a similar extent, although the magnitude of the effects of these three drugs appears to be less than that of barbiturates and benzodiazepines (e.g., [5–7]). The effects of newer AEDs are less well studied, but several reports have suggested that newer AEDs such as gabapentin and lamotrigine may have fewer effects on cognition than do older drugs (e.g., [8,9]). The cognitive effects of AEDs are of particular concern because they are the major therapeutic modality for control of seizures. The assessment of the potential for adverse cognitive effects of AEDs in animals would be of potential benefit in optimizing therapy. Multiple cognitive domains are recognized, including attention, short-term or working memory, long-term memory, and executive function (see, e.g., [1]). We have previously evaluated the effects of AEDs on short-term, or working, memory in nonepileptic rats and found that drugs that directly or indirectly increase GABAergic neurotransmission were particularly prone to produce modest, but statistically significant, disruption of short-term memory [10]. As little is known about the effects of AEDs on other cognitive domains, and attention may be impaired in patients with epilepsy (e.g., [11]), we chose to investigate the effects of AEDs on attention in rats.

The purpose of the present studies was to assess the effects of AEDs on attention in rats as measured by perfor-

* Corresponding author. Fax: +1 317 276 5546.
E-mail address: H.Shannon@Lilly.Com (H.E. Shannon).

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mance under a five-choice serial reaction time (5CSRT) task, a model of attention. Dose–response curves were determined for a broad array of AEDs, including the older AEDs carbamazepine, phenytoin, valproate, and phenobarbital, and the newer AEDs lamotrigine, topiramate, gabapentin, levetiracetam, and tiagabine. For purposes of comparison, dose–response curves were also determined for the anticonvulsant benzodiazepines triazolam and chlordiazepoxide, as well as the muscarinic antagonist scopolamine, which are well known to disrupt cognition in both rats and humans.

2. Materials and methods

2.1. Subjects

Twelve male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN, USA) obtained at approximately 10 to 12 weeks of age were housed individually, with ad libitum access to water, in a large colony room that was maintained on a 12-hour light–dark cycle, where lights were illuminated from 6:00 AM to 6:00 PM. All experimental sessions were conducted during the light cycle. The rats were food deprived to approximately 85% of their free-feeding weights by food presented during experimental sessions and postsession supplemental feeding. All experiments were conducted in accordance with the NIH regulations of animal care covered in *Principles of Laboratory Animal Care*, NIH Publication 85-23, revised 1985, and were approved by the Institutional Animal Care and Use Committee.

2.2. Apparatus

The apparatus consisted of operant conditioning chambers located within sound- and light-attenuating enclosures (Model ENV-009, MED Associates, Inc., St. Albans, VT, USA). Each chamber was equipped with a white house light centered near the top of the front panel and a tone generator near the top on the right-hand side of the front panel. Five response levers were located 2.5 cm above the chamber floor, with 1.5 cm between each response lever. A pellet dispenser was located on the opposite wall and delivered 45-mg Dustless Precision Pellets (Bioserv, Frenchtown, NJ, USA). Operation of the house light, pellet dispenser, and tone generator and recording of data were controlled by a computer using Med-State Notation software (Version 2, MED Associates).

2.3. Procedure

The procedure was similar to that explained in detail previously [12]. Rats were trained to discriminate a brief visual stimulus presented randomly above one of the five response levers. Rats were initially trained to press each of the five response levers to obtain a food pellet; for the first 10 sessions, the correct lever was held constant throughout a session until each animal had experience twice on each lever. During these initial training sessions, the stimulus light above the correct lever remained on until the animal responded on one of the levers or for a maximum of 30 seconds. The schedule contingencies were then changed such that the correct lever, and the presentation of the stimulus light, was presented in randomized blocks across all five response levers. The duration of the stimulus light was gradually reduced to 2 seconds over approximately 20 sessions until the final schedule contingencies were achieved.

Under the final schedule contingencies, each session began with a 1-minute acclimation period during which the chamber was dark and responding had no scheduled consequences. The beginning of each trial was signaled by illumination of the houselight. A response on any lever after the onset of the houselight but before the presentation of a stimulus light immediately terminated the houselight and initiated a 5-second intertrial interval (ITI) during which the chamber was dark and responding had no scheduled consequences. Responses during the prestimulus interval were termed anticipatory responses. In the absence of an anticipatory response, 6.5 (5.0–8.0) seconds after the onset of the houselight, a stimulus light was illuminated above one of the five levers in random order, with each stimulus presented with equal probability. During training sessions, the stimulus light remained illuminated for a maximum of 2 seconds, whereas during test sessions, the stimulus light remained illuminated for a maximum of 0.5 second. On each trial, a response within 5 seconds of the onset of the stimulus (''response window''), on the lever below which the stimulus was presented, immediately terminated the trial, resulted in the presentation of a food pellet, and initiated a 5-second ITI. An incorrect response during the response window immediately terminated the trial and initiated a 5-second ITI. Responses during the ITI were counted but had no scheduled consequences; the next trial began immediately at the end of the 5-second ITI. Sessions were conducted 4 days per week, and each session ended after 30 minutes.

Training sessions were conducted on Monday and Thursday, and test sessions on Tuesday and Friday. No injections were given before training sessions; vehicle or a dose of drug was administered before test sessions. The animals were divided into two groups of six animals each. Group 1 received triazolam, carbamazepine, lamotrigine, gabapentin, and scopolamine, in that order. Group 2 received chlordiazepoxide, phenytoin, valproate, levetiracetam, phenobarbital, tiagabine, and topiramate, in that order. Within each drug series, each rat received each dose of drug and vehicle in a different mixed order.

2.4. Data analysis

Data were recorded separately for each stimulus duration and for each lever during test sessions. Each trial could be terminated by an anticipatory response, a correct