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Specific alterations in the performance of learning and memory tasks in models of chemoconvulsant-induced status epilepticus

Jennifer N. Pearson[a], **Kalynn M. Schulz**[b,d], **Manisha Patel**[a,c,*]

[a] *Neuroscience Program, University of Colorado Anschutz Medical Campus, United States*
[b] *Department of Psychiatry, University of Colorado Anschutz Medical Campus, United States*
[c] *Department of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, United States*
[d] *Medical Research Service, Veterans Affairs Medical Center, Denver, CO, United States*

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Summary Cognitive impairment is a common comorbidity in patients with Temporal Lobe Epilepsy (TLE). These impairments, particularly deficits in learning and memory, can be recapitulated in chemoconvulsant models of TLE. Here, we used two relatively low-stress behavioral paradigms, the novel object recognition task (NOR) and a spatial variation, the novel placement recognition task (NPR) to reveal deficits in short and long term memory, in both kainic acid (KA) and pilocarpine (Pilo) treated animals. We found that both KA- and Pilo-induced significant deficits in long term recognition memory but not short term recognition memory. Additionally, KA impaired spatial memory as detected by both NPR and Morris water maze. These deficits were present 1 week after SE. The characterization of memory performance of two chemoconvulsant-models, one of which is considered a surrogate organophosphate, provides an avenue for which targeted cognitive therapeutics can be tested.

Introduction

Cognitive impairment is a common co-morbidity of the epilepsies and is especially pronounced in patients with medically refractory seizures and patients with Temporal Lobe Epilepsy (TLE). These impairments, including deficits in declarative and spatial memory (Abrahams et al., 1999;

* Corresponding author at: 12850 E. Montview Boulevard V20-C238, Aurora, CO 80045, United States. Tel.: +1 303 724 3604.
E-mail address: Manisha.Patel@ucdenver.edu (M. Patel).

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Guerreiro et al., 2001; Ploner et al., 2000; Viskontas et al., 2000; Elger et al., 2004), contribute significantly to the disability experienced by people with epilepsy. While many clinicians associate cognitive dysfunction specifically with TLE, there is increasing awareness that these deficits are also common in people with other epilepsy syndromes, including extratemporal (Adams et al., 2008) and genetic generalized epilepsies (Adams et al., 2008; Akanuma et al., 2008; Christensen et al., 2007; Filho et al., 2011; Hermann et al., 2008). Whether cognitive deficits are merely the side effect of medication, arise from the seizures themselves, or share a common underlying etiology is the topic of much speculation. Additionally, the threat of progressive cognitive impairment resulting from frequent uncontrolled seizures (Pitkanen and Sutula, 2002) underscores the need for further research on mechanisms of cognitive dysfunction associated with epilepsy. Such research is complicated in the human due to a multitude of factors including genetic background, medication status and history, and other comorbid conditions such as anxiety and depression, any of which can negatively impact cognitive function. Animal models may afford the greatest opportunity to dissect out the roles each of these play in contributing to cognitive impairment associated with epilepsy.

A wide variety of animal models have been developed for the study of specific types of epilepsy (reviewed in Sarkisian, 2001) and although no single animal model can precisely mimic the human condition, several recapitulate important facets of the disease. Perhaps the most commonly studied experimental models of TLE are the chemoconvulsants, kainic acid (KA) and pilocarpine (Pilo). Systemic administration of either KA (an analog of glutamate) or Pilo (a cholinergic agonist) results in a characteristic pattern of intense limbic seizures typically culminating in status epilepticus (SE) or a period of continuous seizure activity. Animals that experience SE-induced by either KA or Pilo are likely to go on to develop spontaneous seizures and become epileptic (Hellier et al., 1998). Chemoconvulsant-induced neuropathology is very similar to TLE-related neuropathology and includes neuronal loss, gliosis, mossy fiber sprouting and synaptic reorganization (Ben-Ari, 1985).

Chemoconvulsant TLE models offer advantages for studying cognitive dysfunction associated with epilepsy. First, use of animal models allows for the identification of potential mechanisms of seizure-induced cognitive damage. Secondly, the chemoconvulsant models allow preclinical testing of therapeutic candidates for cognitive dysfunction occurring in acquired epilepsy (Brooks-Kayal et al., 2013). Additionally, chemoconvulsants such as Pilo, mimic long-term neurochemical and behavioral changes occurring following exposure to chemicals such as nerve agent and/or metabolic poisoning (Jett, 2010). In fact, Pilo has been used as a surrogate of nerve agent neurotoxicity and seizure activity plays a mediating role in its long term toxicity. Therefore the use of chemoconvulsant models to study seizure-induced cognitive dysfunction may yield therapeutic targets beyond TLE.

Behavioral testing in seizure-prone animals represents a series of unique challenges to both selection of paradigms and timing of task performance. Some of the most commonly used paradigms to evaluate learning and memory include the Morris Water Maze (MWM), the Radial Arm Maze (RAM), Contextual Fear Conditioning (CFC), and Delayed Non-Matching to Sample (DNMS). These paradigms have been used to reveal learning and memory deficits in various models of epilepsy including chemoconvulsant-induced SE models, kindling models and some genetic models. However, the use of these tasks to screen for targeted therapies against cognitive deficits associated with the epilepsies may be problematic. First, the use of aversive techniques (water, shocks, and food restriction) to spur performance in these paradigms introduces a possible confound of stress. Furthermore, any drug that affects stress responses or anxiety levels may improve performance and be interpreted as improving learning and memory, when it simply functions as an anxiolytic. Secondly, stress is among the most frequently self-reported precipitants of seizures in patients with epilepsy (Frucht et al., 2000; Spector et al., 2000; Nakken et al., 2005; Haut et al., 2007), so it stands to reason that behavioral tasks that elicit stress may induce seizures in animals with a lowered seizure threshold. It is therefore ideal to include in the cognitive testing battery, tasks that are low-stress to get an accurate representation of learning and memory performance.

The current study tested the effects of two chemoconvulsants, KA and Pilo, on learning and memory performance using two minimally stressful variants of the novel object recognition paradigm, the novel object recognition task (NOR) and the novel placement recognition task (NPR). We also measured locomotion and anxiety-related behavior in the open field in order to assess these parameters during the latent period and also to determine if these factors could account for differences in learning and memory. Finally, we employed the Morris Water Maze (MWM) to allow for comparisons between memory paradigms.

Materials and methods

Animals

Male Sprague-Dawley rats (250—300 g) were purchased from Harlan Laboratories (Indianapolis, Indiana). Upon arrival, animals were housed two per cage in static clear polycarbonate cages with wire bar lids and microisolator air filtration covers. Animals had ad libitum access to both food and filtered water. Room conditions were maintained at 21 °C with a 14:10 light/dark cycle. Animals were treated in accordance with NIH guidelines and all protocols were approved by the IACUC of the University of Colorado Denver.

Chemoconvulsant injections

All animals were handled for approximately 2 min per day starting a week before treatment both to accustom the animals to the investigator and to potentially reduce any stress associated with handling on subsequent testing days. On the day of treatment, animals were randomly assigned to either the control or experimental (KA or Pilo) group. The experimental groups were administered injections of the chemoconvulsants kainic acid (KA, 11 mg/kg, subcutaneously; s.c. Sigma—Aldrich) or Pilocarpine hydrochloride (340 mg/kg, s.c. Sigma—Aldrich) in buffered PBS. Animals treated with Pilo were injected with scopolamine (1 mg/kg, IP) 30 min prior to Pilo to limit peripheral cholinergic effects