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Kainate-induced epileptogenesis alters circular hole board learning strategy but not the performance of C57BL/6J mice

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ABSTRACT

Patients with mesial temporal lobe epilepsy (mTLE) frequently show cognitive deficits. However, the relation between mTLE and cognitive impairment is poorly understood. To gain more insight into epilepsy-associated alterations in cognitive performance, we studied the spatial learning of C57BL/6J mice five weeks after kainate-induced status epilepticus (SE). Typically, structural hippocampal rearrangements take place within five weeks after SE. Mice were monitored by exposing them to four tasks with a focus on spatial memory and anxiety: the circular hole board, modified hole board, novel object-placement task, and elevated plus maze. On the circular hole board, animals showed a higher preference for hippocampus-independent strategies after SE. In contrast, no change in strategy was seen on the modified hole board, but animals with SE were able to finish the task more often. Animals did not have an increased preference for a relocated object in the novel object-placement task but showed an increased locomotion after SE. No indications for altered anxiety were found when tested on the elevated plus maze following SE. These data suggest that the circular hole board is a well-suited paradigm to detect subtle SE-induced hippocampal deficits.

1. Introduction

Cognitive impairment is a phenomenon that often accompanies epilepsy. It may result from antiepileptic drugs and both from the disruption of normal brain functioning during the seizures and from the structural damage that these seizures can cause in the brain in some forms of epilepsy. Cognitive impairment can range from mild to very severe and depends on the brain areas involved in the seizures [1–6]. The deterioration of cognitive abilities is, next to the impact of seizures, decisive for the quality of life. Especially in mesial temporal lobe epilepsy (mTLE), cognitive impairment often occurs in severe forms. In mTLE, seizures originate in the innermost and lowest portion of the temporal lobe, which includes the hippocampus and amygdala. Neuronal damage is often found in the hippocampus [7]. Since the hippocampus is well known for its implication in learning and memory formation, cognitive impairment related to epilepsy is likely to be a consequence of seizure activity and damage in the hippocampus [8–10]. Thus, to study the effects of epileptogenesis on cognition in a controlled setting, behavioral tasks for cognition that depend on a proper functioning of the hippocampus are of most interest. While hippocampal cognitive impairment has often been tested in rats, cognitive tests in mice have been less well-explored. Mice, however, have become increasingly more interesting as a model due to the possibility of genetic manipulations. The Morris water maze test, originally developed for rats, is a commonly used and well-suited test to study hippocampal spatial learning. Studies show that epileptogenesis and experiencing seizures results in increased latency to find the platform in the Morris water maze [11–16].

It should be noted, however, that the use of the Morris water maze for studying mice introduces a potentially confounding factor. Because of their aversion to water [17], mice experience stress and anxiety in the test. As stress and anxiety are importantly involved in many neurological disorders, including epilepsy [18–23], the additional aversive component will influence the experimental outcome [24]. In addition, the C57BL/6J mouse strain tends to display floating behavior in the Morris water maze [25], altogether making this task inappropriate for

Abbreviations: mTLE, mesial temporal lobe epilepsy; SE, status epilepticus; KA, kainate or kainic acid; CHB, circular hole board; MHB, modified hole board; EPM, elevated plus maze; NOP, novel object placement.

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monitoring hippocampal spatial learning in these mice. However, other behavioral tasks to test hippocampal functioning in mice are available, and several of them have indeed been used to monitor seizure-induced cognitive impairments in different mouse strains (Table 1). Both the strain and behavioral model used are of importance, and in general, studies show decreased spontaneous alterations in the Y-maze [15,26], a decreased latency in the passive avoidance task [11–13,15,27], and an impaired retention transfer latency [27], all pointing towards cognitive impairments. Thus, the processes that take place in an epileptic brain and after seizures can have a significant effect on cognitive and emotional behavior including spatial memory and anxiety [3,28].

To date, little is known about the cognition and anxiety of male C57BL/6J mice specifically after kainate (KA)-induced status epilepticus (SE). The sequelae of KA-induced SE mimic many characteristics of mTLE, and this model has been used for decades [29] to investigate this form of epilepsy. For behavioral tasks, we chose the circular hole board, the modified hole board, and the novel object-placement task to assess hippocampus-dependent spatial memory performance. These tasks, in contrast to the Morris water maze, avoid stressful swimming [30]. Since stress is known to affect memory formation [31–36], we wanted to eliminate stress as a confounding factor as much as possible. As we noticed behavior that could be described as anxiousness during these tasks, we also included the elevated plus maze test in the evaluation, which is a commonly used task to measure anxiety [37–40]. All behavioral tasks took place at least 5 weeks after the induction of SE to assure that neuronal structural rearrangements have taken place as a consequence of kainate simulation [4,41–46]. We showed that the circular hole board is a well-suited paradigm to detect subtle hippocampal deficits in male C57BL/6J mice.

2. Material and methods

2.1. Subjects

Male C57BL/6J mice (n = 76; Janvier, the Netherlands) were randomly assigned to treatment groups and behavioral tasks. Animals were housed individually 24 h before the start of SE in a normal cage with a tunnel and nesting material. All animals were maintained on a 12/12-hour light/dark cycle and had access to food and water ad libitum. Animals were handled daily prior to the induction of SE. Since stress-released corticosterone is known to affect cognitive performance and anxiety-related behavior [33–36,46], all cognitive tasks were performed before the onset of the circadian peak of endogenous corticosterone levels (i.e., within 6 h after lights went on). In the experimental room, a radio producing 20 dB of background noise was present and the light intensity was 90 lx as described previously [40,47]. A schematic timeline of the behavioral experiments is shown in Fig. 1. All experiments were approved by the committee on Animal Health and Care from Leiden University, the Netherlands, in accordance with the EC Council Directive of September 2010 (2010/63/EU).

2.2. Induction of seizures

Epileptic seizures were induced by repeated injections of kainate (KA; Sigma; solved as 1.2 mg/ml in saline) as described previously [48]. Kainate administration was started 1 h after the light went on. The starting dose was 18–24 mg/kg body weight, and subsequent injections of 6 mg/kg body weight were given every 30 min until seizures occurred. Seizure behavior was visually observed and scored according to a modified Racine's scale [7,49,50]. Injections were paused when

Table 1
Literature overview of anxiety (ANX) and learning and memory (SP) tasks performed in adult mice after SE. Red arrows show increased anxiety or increased memory; green arrows show decreased anxiety or decreased performance in learning/memory tasks.

Behavioral test	Category	SE method	Result	Strain	Sex	Ref.
Elevated plus maze	ANX	KA intrahippocampal	=	NMRI	♀	[11]
		Pilocarpine	=	NMRI	♀	[12]
		Pilocarpine	=	C57BL/6NCrl	♀	[14]
		Pilocarpine	=	NMRI	♀	[13]
		Lithium–pilocarpine	=	NMRI	♀	[13]
Hole board		KA intrahippocampal	=	NMRI	♀	[11]
		Pilocarpine	↑	NMRI	♀	[12]
		Pilocarpine	=	C57BL/6NCrl	♀	[14]
Novel object exploration		KA intrahippocampal	=	NMRI	♀	[11]
		Pilocarpine	↑	NMRI	♀	[12]
		Pilocarpine	=	C57BL/6NCrl	♀	[14]
Open field		KA intrahippocampal	=	NMRI	♀	[11]
		Pilocarpine	↑	NMRI	♀	[12]
		Pilocarpine	↑	C57BL/6NCrl	♀	[14]
		Pilocarpine	↑	NMRI	♀	[13]
		Lithium–pilocarpine	↑	NMRI	♀	[13]
Morris water maze	SP	KA intrahippocampal	↓	NMRI	♀	[11]
		KA intrahippocampal	↓	C57BL/6J	♂	[51]
		Pilocarpine	↓	NMRI	♀	[12]
		Pilocarpine	↓	C57BL/6J × FVB	♀♂	[16]
		Pilocarpine	↓	C57BL/6NCrl	♀	[14]
		Pilocarpine	↓	NMRI	♀	[13]
		Lithium–pilocarpine	↓	NMRI	♀	[13]
Water maze		Pilocarpine	↓	Swiss	♂	[57]
		Pilocarpine	↓	Std–ddY	♂	[15]
Y-maze		Pilocarpine	↓	Std–ddY	♂	[15]