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Spatial learning deficits and emotional impairments in pentylenetetrazole-kindled rats

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Abstract

Pentylenetetrazole (PTZ) is a chemical kindling agent used to examine the efficacy of potential anticonvulsants in rats. However, the extent to which PTZ mimics postseizure symptoms of epilepsy has not been thoroughly examined. This study assessed whether PTZ-induced seizures produce cognitive and emotional deficits that mimic those observed in many epileptic patients. Rats were given 30 mg/kg PTZ or vehicle (intraperitoneally) every other day for 28 days. Those rats exhibiting consistent seizure activity were tested for learning ability and emotional reactivity, beginning 1 week following a single challenge dose of PTZ. Rats given PTZ made more reference memory errors in a radial arm water maze task, and exhibited emotional abnormalities in the forced swim test, the systematic handling test, and the open-field exploratory maze. Histological analysis revealed neuronal loss in the CA1 area and increased mossy fiber sprouting in the dentate gyrus, similar to what is observed in human epilepsy. These results indicate that PTZ kindling provides a useful model of postseizure dysfunction, which can serve as a screen for potential treatments for those cognitive, emotional, and neuropathological deficits that resemble those symptoms observed in human epilepsy.

Keywords: Pentylenetetrazole; Kindling; Spatial learning; Radial arm water maze; Behavior; Epilepsy; Fear; Depression; Aggression; Open field

1. Introduction

Epilepsy is characterized by recurrent seizures due to excessive discharge of cerebral neurons. These recurrent seizures can produce cognitive deficits, emotional impairments, and psychosocial problems [1–4]. Seizure-induced cognitive impairments have been reported for both children and adults [1,5–10]. Furthermore, specific deficits in spatial reference memory and short-term memory have also been reported in patients with temporal lobe epilepsy [11,12]. Using the nine-box maze test, which is similar to the radial-arm-maze task, Abrahams et al. [11] found both working and reference memory deficits in patients with epilepsy.

In addition to problems with memory and other cognitive processes, many patients with epilepsy have also been diagnosed with affective and personality disorders [3,13]. Of these disorders, depression and anxiety are most common, with more than 50% of patients with epilepsy being diagnosed with depression [14], many of these being comorbid with anxiety [13]. Depression has been described during the prodromal, ictal, postictal, and interictal periods, with interictal depression occurring most frequently [15]. As with depression, patients with epilepsy have also been reported to have a high incidence of aggression, especially during the postictal period [15,16]. Aggression can also occur in the context of postictal psychosis, which, when present, usually starts a few days after the occurrence of seizures [17].

Kindling models of epilepsy have been developed to test potential antiepileptic drugs and to define more precisely the possible etiology of the disorder. Kindling can

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be defined as the repeated electrical or chemical stimulation of neuronal pathways that eventually leads to a progression of behavioral and electrographic seizures [18]. A commonly used kindling model is the administration of pentylenetetrazole (PTZ) to rats [19–25]. PTZ is a central nervous system convulsant that is thought to act at the picrotoxin (PTX) site of the γ-aminobutyric acid type A ($GABA_A$) receptor, blocking the GABA-mediated Cl^- influx through an allocentric interaction in the Cl^- channel, leading to neuronal membrane depolarization and, consequently, the propagation and maintenance of seizure activity [26].

Although the PTZ kindling model has proven to be effective in producing seizures and, thus, for testing the efficacy of drugs in reducing convulsions, its utility as a screen for testing treatments of postseizure cognitive and emotional problems has not been thoroughly studied. Specifically, the extent to which PTZ kindling produces the types of postseizure symptoms of affective disorders and learning deficits that are observed in many patients with epilepsy has not been systematically examined. For example, there is some indication that PTZ kindling produces symptoms of anxiety [27,28], but there is little, if any, indication as to whether it produces other emotional alterations, such as depression and aggression, which are observed in patients with epilepsy. In addition, the degree to which PTZ produces postseizure cognitive deficits is also unclear, especially to the degree it affects spatial learning and to what extent it differentially affects reference and working memory. For example, there is ample evidence for PTZ-induced postseizure learning deficits on nonspatial tasks [23,29–33], but results from the few studies using spatial learning paradigms are inconsistent. Specifically, Hamm and colleagues [34] found spatial learning deficits in PTZ-treated rats in the Morris water maze (MWM) task, whereas Lamberty and Klitgaard [27] did not.

The purpose of the present study was to further investigate whether PTZ kindling mimics seizure-induced cognitive and emotional problems that are observed in many patients with epilepsy. To this end, we assessed the effects of PTZ-induced seizures on: (1) reference and working memory on a spatial learning task, using the radial arm water maze (RAWM); (2) depression, using the forced swim task; (3) aggression, using the systematic handling test; and (4) anxiety, using the exploratory open-field maze test.

2. Methods

2.1. Animals

Twenty-two male Sprague–Dawley rats (250–300 g) were individually housed in wire cages and were given food and water ad libitum. The animals were kept under controlled laboratory conditions under a 12-hour light/dark cycle (0800–2000) cycle. Care and use of the animals were in strict adherence to guidelines of the National Institute of Health and of Central Michigan University's Institute for Animal Care and Use Committee.

2.2. Experimental protocol

An overview and timeline for the various tests are shown in Fig. 1. Care was taken to minimize potential effects of one test on another. Most tests were conducted on separate days, and ample time between each test was provided to minimize any potential confounding effects. For all behavioral and histological evaluations, the group identity of each rat was concealed to the evaluator, so that the experimenters were blind to the group identity of the rats, to control for possible experimenter bias.

2.3. Kindling

Rats were randomly assigned to one of two conditions: (1) PTZ group ($n = 14$), in which rats were injected intraperitoneally with PTZ (30 mg/kg in 0.9% saline) and (2) the control group ($n = 8$), in which rats received intraperitoneal injections of the vehicle. Injections were administered at 1400 hours every other day over a 4-week period (i.e., a total of 14 injections). Immediately after injections, the seizure activity was monitored for 30 minutes in a clear Plexiglas box (100 cm wide × 100 cm long × 50 cm high) with a matted floor. Animals were considered to be fully kindled if they had at least three consecutive tonic–clonic seizures during the 4-week testing period. One week after the last PTZ kindling injection, these rats received a final challenge dose of PTZ (30 mg/kg) to check the persistence of enhanced susceptibility to the convulsant. Only those PTZ-treated rats that had tonic–clonic seizures following the challenge dose ($n = 8$) were used in the remainder of the study. Control rats received injections of saline instead of the PTZ challenge dose.

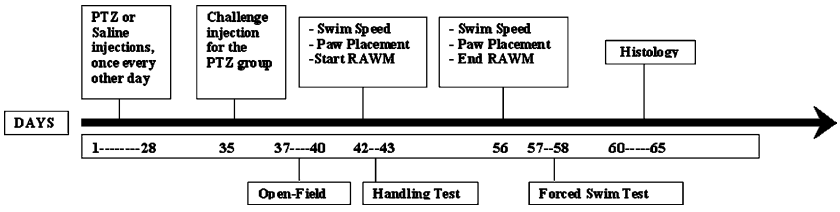

Fig. 1. Overview and timeline for the procedures used in this study. Testing sessions were spaced appropriately to allow for sufficient rest time during the days when multiple tests were conducted (see text). Most tasks were conducted on separate days to minimize the potential confounding effects of one test interfering with subsequent behavior measures.