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Review

Animal models of temporal lobe epilepsy following systemic chemoconvulsant administration

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HIGHLIGHTS

- We review the kainic acid and pilocarpine models of temporal lobe epilepsy.
- We assess status epilepticus in different species and strains.
- We present the general events occurring during the latent and chronic periods.
- We describe the neuropathological changes in these models.
- We discuss the effect of anti-epileptic drugs on spontaneous seizures.

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ABSTRACT

In order to understand the pathophysiology of temporal lobe epilepsy (TLE), and thus to develop new pharmacological treatments, in vivo animal models that present features similar to those seen in TLE patients have been developed during the last four decades. Some of these models are based on the systemic administration of chemoconvulsants to induce an initial precipitating injury (*status epilepticus*) that is followed by the appearance of recurrent seizures originating from limbic structures. In this paper we will review two chemically-induced TLE models, namely the kainic acid and pilocarpine models, which have been widely employed in basic epilepsy research. Specifically, we will take into consideration their behavioral, electroencephalographic and neuropathologic features. We will also evaluate the response of these models to anti-epileptic drugs and the impact they might have in developing new treatments for TLE.

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1. Introduction

The unpredictable and recurrent nature of seizures associated to temporal lobe epilepsy (TLE) is the most disabling feature of this neurological disorder. To further complicate matters, seizures in TLE are often resistant to anti-epileptic drugs. Surgical resection of the epileptogenic tissue is thus offered as an alternative, but it is costly and at times impractible. To fully understand TLE pathophysiology and to develop new therapeutic approaches, animal models that reproduce the electroencephalographic, behavioral and neuropathological features of this epileptic disorder have been developed over the last four decades. In this review, we will take into analysis the two main animal models of TLE that use the systemic administration of chemoconvulsants. These procedures induce an initial brain injury (*status epilepticus*, SE) that is followed by a latent period and the recurrence of spontaneous seizures originating from the temporal lobe. These models have been extensively used in research because of their high level of similarity with the human disease.

One of these models uses kainic acid, a cyclic analog of L-glutamate and an agonist of the ionotropic kainic acid receptors. Although it was first shown by Nadler et al. (1978) that hippocampal pyramidal cells are highly sensitive to damage induced by kainic acid, the use of this drug as a model of TLE was originally proposed by Ben-Ari and Lagowska (1978) and Ben-Ari et al. (1979), who reported that intra-amygdaloid injections of kainic acid in rodents induce behavioral seizures and produce neuropathological lesions that are similar to those occurring in some patients with epilepsy, i.e., neuronal degeneration that mainly occurs in the CA3 region of the dorsal hippocampus. This initial SE was also followed days later by the occurrence of spontaneous seizures (Cavalheiro et al., 1982). The other model uses pilocarpine, a cholinergic muscarinic agonist. The pilocarpine model was first described by Turski et al. (1983), who showed that systemic intraperitoneal administration of pilocarpine in rodents was followed by a sequence of automatisms and motor limbic seizures evolving into *status epilepticus*. Analysis of the brain of these animals revealed widespread damage in the olfactory cortex, amygdala, thalamus, neocortex, hippocampus and substantia nigra (Turski et al., 1989). As with kainic acid, pilocarpine-treated animals showed spontaneous seizures approximately 2 weeks after the initial *status epilepticus* (Turski et al., 1989). These findings thus suggested that both kainic acid and pilocarpine treatments represented valid TLE models since they reproduce the typical histopathological alterations and spontaneous chronic seizures seen in epileptic patients.

In this review we will compare the kainic acid and pilocarpine models by addressing the three critical time points of TLE that are the initial *status epilepticus*, the latent and the chronic period. We will also compare the neuropathological changes associated to each model and evaluate their response to anti-epileptic drugs. Finally, we will address the potential impact of these two models for developing new TLE therapies.

2. Status epilepticus

Status epilepticus is defined as a period of seizure activity lasting for at least 30 min during which full consciousness does not recover (Lowenstein et al., 1999; Scott, 2014). It usually evolves through two stages. The first stage is characterized by generalized convulsive tonic-clonic seizures whereas the second stage is associated to minor behavioral symptoms concomitant to continuous electrical discharges, increase in intracranial pressure and decrease in cerebral blood flow (Cherian and Thomas, 2009). It is thus a medical condition that needs to be treated rapidly since it is life-threatening. Moreover, animal studies have shown that a prolonged duration (more than 30 min) of seizure activity may lead to permanent neuronal damage and synaptic reorganization (Lowenstein et al., 1999), conditions that are often associated to the development of "chronic" epilepsy.

Chemoconvulsant-induced TLE models reproduce this initial brain injury. In adult animals, the administration of a single intraperitoneal dose of kainic acid (6–15 mg/kg) or of pilocarpine (360–400 mg/kg) (Curia et al., 2008; Lévesque and Avoli, 2013) can trigger *status epilepticus*. In both models, behavioral symptoms are observed within 1 h after administration of the chemoconvulsant, and are characterized by a catatonic posture and automatisms that progress to myoclonic twitching of the head and limbs, followed by severe limbic seizures and rear falling (Sperk et al., 1983; Strain and Tasker, 1991; Turski et al., 1983, 1989).

2.1. Mortality rates

In the kainic acid model, the mortality ranges from 5 to 30% but it can be decreased with the administration of multiple doses of 5 mg/kg until the occurrence of *status epilepticus* (Lévesque and Avoli, 2013). Mortality rates in the pilocarpine model are higher since approximately 30–40% of treated animals will not survive status epilepticus (Curia et al., 2008). These rates can however be significantly reduced with the administration of lithium (127 mg/kg, i.p.), 24 h before the injection of pilocarpine (Clifford et al., 1987; Curia et al., 2008; Müller et al., 2009). The dose of pilocarpine necessary to induce *status epilepticus* when it is administered after a pre-treatment with lithium however needs to be to decreased to 30 mg/kg in rats, since they show an increased susceptibility to the chemoconvulsant (Curia et al., 2008; Müller et al., 2009). The lithium–pilocarpine model is associated to behavior abnormalities, histopathological changes and EEG activity that are similar to those observed in the pilocarpine model (Curia et al., 2008; Müller et al., 2009). Using multiple 10 mg/kg doses of pilocarpine can also be used to decrease mortality rates and increase the proportion of treated animals that will develop spontaneous seizures (Curia et al., 2008; Sharma et al., 2007). However, combining a pre-treatment with lithium at 30 mg/kg and multiple doses of pilocarpine at 10 mg/kg until the occurrence of *status epilepticus* is the most effective method, since it can reduce mortality rates to 7%