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Review

The kainic acid model of temporal lobe epilepsy

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ABSTRACT

The kainic acid model of temporal lobe epilepsy has greatly contributed to the understanding of the molecular, cellular and pharmacological mechanisms underlying epileptogenesis and ictogenesis. This model presents with neuropathological and electroencephalographic features that are seen in patients with temporal lobe epilepsy. It is also characterized by a latent period that follows the initial precipitating injury (*i.e.*, *status epilepticus*) until the appearance of recurrent seizures, as observed in the human condition. Finally, the kainic acid model can be reproduced in a variety of species using either systemic, intrahippocampal or intra-amygdaloid administrations. In this review, we describe the various methodological procedures and evaluate their differences with respect to the behavioral, electroencephalographic and neuropathological correlates. In addition, we compare the kainic acid model with other animal models of temporal lobe epilepsy such as the pilocarpine and the kindling model. We conclude that the kainic acid model is a reliable tool for understanding temporal lobe epilepsy, provided that the differences existing between methodological procedures are taken into account.

Contents

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1. Introduction

According to the World Health Organization, epilepsy is the most prevalent neurological disorder, with a prevalence of over 50 million and an incidence of 2.4 million per year. Partial epileptic disorders represent 60% of these cases, with temporal lobe epilepsy (TLE) being the most common type. Symptoms in TLE consist of partial seizures that originate from the hippocampus, entorhinal cortex or amygdala many years after an initial brain insult such as *status epilepticus* (SE), encephalitis or febrile convulsions. Many antiepileptic drugs are currently available to control or to reduce seizure occurrence, but approximately one third of patients are refractory to medication, making TLE one of the most refractory form of partial epilepsy in adults (Engel et al., 2012). In such patients, surgical resection of the epileptic tissue remains the only therapeutic alternative. However, the seizure onset zone and possible post-surgical neurological deficits must be assessed with multiple and costly tests including pre-surgical invasive procedures such as intracranial EEG recordings.

Patients with TLE typically show hippocampal sclerosis, characterized by selective neuronal loss in the CA1/CA3 region of the hippocampus and the hilus, along with granule cell dispersion and aberrant mossy fiber sprouting in the molecular layer of the dentate gyrus (Berkovic et al., 1991; Buckmaster, 2012; Gloor, 1997; Jackson et al., 1990; Thorn, 1997). Removing the sclerotic hippocampus will reduce seizure occurrence but still approximately 30% of patients are not seizure-free after surgery because of insufficient resection of the epileptic tissue. Indeed, it was hypothesized that TLE may involve a broad extrahippocampal, or even extratemporal, network (Bartolomei et al., 2008; Harroud et al., 2012; Najm et al., 2013; Spencer, 2002; Spencer and Spencer, 1994) since performing a total resection of the hippocampus is more effective in controlling seizures compared to a lobectomy restricted to only the anterior part of the temporal lobe (Wyler et al., 1995). Finally, in some patients, the seizure onset zone cannot be clearly identified and thus they become poor candidates for surgical treatment.

Taken together, these clinical findings put further emphasis on the need to use experimental models of TLE to replicate the histopathological, electroencephalographic and behavioral features encountered in this neurological disorder in order to answer many unresolved questions; these include the localization and extent of the seizure onset zone as well as the mechanisms underlying epileptogenesis. The identification of the seizure onset zone is especially important for the surgical treatment of TLE while understanding epileptogenesis is crucial for establishing the evolution of this epileptic disorder since "seizures may beget seizures", by inducing additional neuronal damage or aberrant synaptogenesis (Ben-Ari et al., 2008).

Although there is no experimental model that reproduces all the features of TLE, some models have been extensively used over the past decades because of their high level of similarity with human epilepsy. One of these is the kainic acid (KA) model, that was originally discovered by Ben-Ari (Ben-Ari and Lagowska, 1978; Ben-Ari et al., 1979a). In these initial studies, they showed that intra-amydaloid injections of KA induce behavioral seizures and produce neuropathological lesions that are similar to those occurring in patients with TLE (*i.e.*, neuronal degeneration in the CA3 region of the dorsal hippocampus).

In this paper, we will review the results obtained from *in vivo* studies in which KA was administered intracerebrally or systemically. For each method, we will summarize their associated behavioral, electroencephalographic and neuropathological features. In addition, we will compare the epileptogenic properties of KA following intracerebral or systemic injection as well as the influence of the age of the animals on both KA-induced seizures and associated neuropathological changes. Finally, we will compare the KA model to two other models of TLE, namely the pilocarpine model and the kindling model.

2. Kainic acid

KA is a cyclic analog of L-glutamate and an agonist of ionotropic KA receptors. It was isolated and extracted in the early 1950s, from a red algae (*Digenea simplex*) found in tropical and sub-tropical waters (Murakami et al., 1953). It was named digenic acid but this term was later changed to KA in order to avoid confusion with the other derivatives of Digenea (Nadler, 1979). KA was first meant to be used as an ascaricide to eradicate ascariasis, a disease caused by the parasitic worm *Ascaris lumbricoides*. However, it was later found that it induced in rats prolonged excitatory responses in cortical neurons following microiontophoretic application (Shinozaki and Konishi, 1970). It became thus clear that KA could be used as a potent analog of glutamate, and that it could induce robust depolarizations and eventually cell death, a central phenomenon to TLE (Bloss and Hunter, 2010; Vincent and Mulle, 2009). This opened the path to the identification of new glutamate receptor subtypes, a better characterization of glutamatergic structures and pathways, and eventually the development of a new animal model of temporal lobe epilepsy characterized by a latent period followed by refractory spontaneous seizures, as in human TLE (Ben-Ari, 1985; Ben-Ari and Cossart, 2000; Nadler, 1981). The use of KA also led to a better understanding of various neurodegenerative disorders such as Parkinson's disease (Meredith et al., 2009), Huntington's disease (Coyle and Schwarcz, 1976; Coyle et al., 1977), Alzheimer's disease (Hynd et al., 2004), amyotrophic lateral sclerosis (Redler and Dokholyan, 2012) and multiple sclerosis (Pitt et al., 2000). These neurological conditions, will, however, not be discussed in this review.

2.1. Kainic acid receptors

During the past thirty years, many studies have successfully mapped the localization of KA receptors (KARs). They can be found at different levels of expression in the amygdala (Rogawski et al., 2003), entorhinal cortex (Patel et al., 1986), basal ganglia (Jin and Smith, 2011) and cerebellum (Wisden and Seeburg, 1993). They are also highly expressed in the hippocampus where they are located both presynaptically and postsynaptically (Bloss and Hunter, 2010). KA1 subunits (actually known as GluK4, according to the International Union of Basic Science and Clinical Pharmacology Database (IUPHAR-DB)) (Sharman et al., 2013) are highly expressed in CA3 pyramidal cells but only weakly expressed in CA1 pyramidal cells (Bahn et al., 1994; Werner et al., 1991; Wisden and Seeburg, 1993). KA2 (GluK5) subunits are instead highly expressed in both CA1 and CA3 pyramidal cells (Bahn et al., 1994; Wisden and Seeburg, 1993). Therefore, the high affinity of KA1 and KA2 receptors to glutamate and their high rates of expression in the CA3 region of the hippocampus render this region highly susceptible to the excitotoxic damage induced by KA and often makes the hippocampus the seizure onset zone in this model (Ben-Ari and Cossart, 2000; Lévesque et al., 2009; Lothman et al., 1981). More specifically, the ictogenic properties of CA3 and, more generally, its capacity to generate synchronized activities following KA administration may be attributed to the activation of pyramidal neurons *via* the high-affinity KARs in the mossy fiber synaptic region that correspond to the *stratum lucidum* (Ben-Ari and Cossart, 2000).

Other KAR subunits (such as the GluR5 and GluR6 subunits or GluK1 and GluK2, respectively) also contribute to the excitatory action of KA; GluR6 are highly expressed in CA3 pyramidal cells (Bahn et al., 1994) while GluR5 are highly expressed in GABAergic interneurons in both CA1 and CA3 subfields (Bloss and Hunter,