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Animal models of temporal lobe epilepsy following systemic chemoconvulsant administration

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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.

Keywords

Animal models; Kainic acid; Pilocarpine; Temporal lobe epilepsy

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 impracticable. To fully understand TLE patho-physiology and to develop new therapeutic approaches,

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Conflict of interest

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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 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% and a high proportion of animals (85%) will develop spontaneous seizures (Glien et al., 2001).

2.2. Electroencephalographic activity

In the kainic acid model, the hippocampus and the amygdala are often the sites of origin of electrographic seizures, which then propagate to the neocortex (Ben-Ari et al., 1981; Lévesque et al., 2009; Turski et al., 1983, 1989). Ictal discharges indeed appear in the CA3 region of the hippocampus and in the amygdala, and rapidly propagate to the thalamus, the CA1 region and the frontal cortex (Ben-Ari et al., 1981). These ictal discharges are, however, observed only on the EEG and are not associated to any clinical signs, besides wet-dog shakes. Hippocampal EEG activity in these animals is also characterized by rhythmic patterns in the gamma frequency range (25–30 Hz) (Lothman et al., 1981; Medvedev et al., 2000). Following pilocarpine administration, theta rhythm and isolated interictal spikes are first observed in the hippocampus, and followed by low voltage fast activity in the neocortex (Turski et al., 1989). Seizures then start from the hippocampus and rapidly propagate to the amygdala and neocortex (Turski et al., 1989).

Status epilepticus will spontaneously remit after 5–6 h after pilocarpine or kainic acid administration (Curia et al., 2008; Fritsch et al., 2010). However, in order to reduce inter-

animal variability, mortality rates as well as to design specific experimental protocols, the *status epilepticus* can be stopped in both models after 30–120 min by concomitant administration of ketamine (50 mg/kg i.p or s.c.) and diazepam (20 mg/kg i.p or s.c.) (Martin and Kapur, 2008; Vermoesen et al., 2010). A synergistic or superadditive action of diazepam and ketamine is thought to contribute to the suppressive effect of this drug cocktail on *status epilepticus*, since when they are administered alone at the doses mentioned above, no effect is observed (Martin and Kapur, 2008). Interestingly, ethanol potentiates the effect of diazepam to stop status epilepticus (Klein et al., 2014).

2.3. The effect of strain and the environment

The kainic acid and pilocarpine procedures are well established for rats. However, it is known that the effect of chemoconvulsant differs between rat strains, since mortality rates and neuronal damage are higher in Long–Evans and Wistar strains as compared to Sprague–Dawley rats (Curia et al., 2008). To make things more complex, animals from the same supplier, but coming from different breeding colonies, may have different sensitivities (Langer et al., 2011). The way animals are treated and fed by the supplier and the way they are handled/stored at one's institution may also affect to probability to trigger status epilepticus and influence mortality rates.

Using mice adds another layer of complexity, since some strains are highly sensitive to chemoconvulsants agents. For instance, C57 and C3H mice show high seizure-related mortality rates (57%) following a single injection of kainic acid, compared to 129/SvJ or 129/SvEms mice in which kainic acid is associated to a mortality rate between 0 and 8% (McKhann et al., 2003). C57 and C3H strains are also more susceptible to show long and severe seizures in contrast to 129/SvJ and 129/SvEms mice, but are less sensitive to neuronal loss and less likely to develop mossy fiber sprouting (McKhann et al., 2003; Schauwecker and Steward, 1997). However, these findings cannot be generalized to pilocarpine, since C57 mice are highly sensitive to neuronal injury following pilocarpine (Schauwecker, 2012).

Also, one may have to struggle weeks before getting stable results with kainic acid because mice are less likely to develop spontaneous seizures compared to rats (McKhann et al., 2003). However, they are more likely to show spontaneous seizures following pilocarpine (Cavalheiro et al., 1996), as it is observed in rats. It is also important to note that *status epilepticus* often starts minutes before overt behavioral signs. Continuous EEG recordings are thus necessary to determine when *status epilepticus* starts, which is critical to determine when to stop it. This may also constitute a source of variability in the results when using mice.

Finally, the environment (animal facility or laboratory) and the way animals are handled play a key role in the success rate. Rodents are nocturnal animals, and we tend to trigger *status epilepticus* during the light phase, when they are less active. The threshold to trigger seizures is clearly regulated in a circadian manner (Oliverio et al., 1985). Whether *status epilepticus* induction and survival rate are regulated in a circadian manner remains to be determined.

The allostatic load also plays a key role. Stress accumulation can have a major outcome. It is advisable to wait at least one week after receiving the animals. It is also highly advisable to start social contact with the animals, which will reduce the stress when handling them for the injection of chemoconvulsants, and to take care of animals during the recovery phase by rehydrating them as often as necessary.

The main advantage of the pilocarpine over the kainic acid model rests on its ability to rapidly induce *status epilepticus* (and its reduced cost as compared to kainic acid). Few injections are necessary since a single initial dose of pilocarpine followed by a second half dose (after 30 min, if needed) is sufficient to produce *status epilepticus*. In the kainic acid model, multiple injections at 1 h interval may be necessary to induce *status epilepticus*, which could make the duration of the experiment lasting between 6 and 8 h (Hellier et al., 1998). However, kainic acid treated animals are more likely to survive SE (Covolan and Mello, 2000).

3. Latent period

The latent (at times, but erroneously, called ‘silent’) period is defined as the time between the initial brain insult (i.e., in the case of our models the SE) and the clinical manifestation of the first seizure. This seizure-free period can last for many years in humans (French et al., 1993; Mathern et al., 1995) but it is in the range of days to weeks in animals made epileptic by using chemoconvulsants (Bortel et al., 2010; Chauvière et al., 2012; Drexel et al., 2012; Goffin et al., 2007; Lévesque et al., 2011, 2012; Mello et al., 1993; Rose Priel et al., 1996; Salami et al., 2014; Turski et al., 1989; White et al., 2010; Williams et al., 2006). During this latent period, although there are no clinical signs of epileptic activity, alterations in neuronal and glial cell structure and function are presumably occurring. Axon sprouting, structural changes in pre and postsynaptic receptors, changes in voltage-gated ion channels, alterations of homeostatic mechanisms and neuronal degeneration have all been associated to epileptogenesis (Scharfman and Pedley, 2007). Whether these abnormal processes are caused by the initial brain injury or were already present in some predisposed individuals is still a matter of debate.

The latent period could also represent the time it takes before the system becomes stable, as seizure frequency follows a sigmoid function during that time (Williams et al., 2009). It is only at the end of this sigmoid function that seizures can show clustering and circadian regulation (Kadam et al., 2010). Regardless of semantic issues, it is important to keep in mind that, as in humans, epilepsy is a constantly evolving phenomenon (Pitkänen and Sutula, 2002).

3.1. Interictal spikes

In the kainic acid model, the duration of the latent period spans between 10 and 30 days after the injection (Chauvière et al., 2012; Cherubini et al., 1983; Drexel et al., 2012; Lado, 2006; Petkova et al., 2014; Sharma et al., 2007; White et al., 2010; Williams et al., 2006) but in some experiments it may last up to 5 months after treatment (Williams et al., 2006). During this period, depth EEG recordings show interictal spikes in temporal lobe regions (Chauvière et al., 2012; Suárez et al., 2012; White et al., 2010; Williams et al., 2006; Zhang

et al., 2011). Using systemic injections of kainic acid, White et al. (2010) reported that the rate of occurrence of interictal spikes before the first seizure is correlated with seizure frequency. More specifically, rats that develop spontaneous seizures had higher rates of interictal spikes compared to rats that did not develop chronic epilepsy. In a more recent study, Chauvière et al. (2012) reported that different types of interictal spikes can be recorded in the hippocampus of kainic acid-treated animals during the latent period. They observed that before the occurrence of the first seizure, the frequency, duration and amplitude of type 1 spikes (interictal spikes followed by a long lasting wave) started to decrease whereas the frequency of type 2 spikes (interictal spikes without a wave) increased. According to these authors, type 1 spikes would correspond to neuronal activity from large populations of excitatory and inhibitory cells, whereas type 2 spikes would reflect the activity of excitatory cells at a more local level. The decline of type 1 spikes and the increase in frequency of type 2 spikes before the occurrence of the first spontaneous seizure was attributed to the progressive alteration of inhibitory circuits and the buildup of epileptic circuits during epileptogenesis.

In the pilocarpine model, the duration of the latent period is similar to that reported in kainic acid-treated animals, since the latent period lasts on average between 4 and 40 days after its administration (Bortel et al., 2010; Cavalheiro et al., 1991; Chauvière et al., 2012; Lévesque et al., 2011, 2012; Liu et al., 1994; Soukupová et al., 2014). As it was shown in kainic acid-treated animals, interictal spikes occur in the temporal lobe regions of pilocarpine-treated animals during this time period (Bortel et al., 2010; Chauvière et al., 2012; Salami et al., 2014). Also, type 1 spikes decrease in amplitude, frequency and duration whereas the frequency of type 2 spikes increases before the onset of the chronic period (Chauvière et al., 2012).

3.2. Effect of electrode implantation

Interestingly, in both animal models, the duration of the latent period differs between animals that are implanted for depth EEG recordings before or shortly after status epilepticus and those that are not implanted. In pilocarpine-treated rats, spontaneous seizures in implanted animals occur sooner (i.e., 4–6 days; Bortel et al., 2010; Lévesque et al., 2011; Lévesque et al., 2012; Salami et al., 2014) than in animals that are not implanted (i.e., 11 days to 6 weeks after status epilepticus; Cavalheiro et al., 1991; Liu et al., 1994; Soukupová et al., 2014). In the kainic acid model, animals that are implanted with depth electrodes before kainic acid treatment have a latent period of approximately 15 days (White et al., 2010; Williams et al., 2009), compared to 77 days in non-implanted animals (Hellier et al., 1998). Two possible causes may underlie this phenomenon. First, non-convulsive seizures (only visible on the EEG and missed by experimenters using non-implanted animals) occur sooner than convulsive seizures (Bortel et al., 2010; Goffin et al., 2007; Lévesque et al., 2011; Williams et al., 2009). Since the end of the latent period is based on the first spontaneous seizure (non-convulsive or convulsive), animals with depth EEG recordings are more likely to have a shorter latent period. These results thus emphasize the need to perform continuous depth EEG recordings in epileptic animals early after *status epilepticus* since the duration of the latent period may be overestimated. Second, the implantation of electrodes might induce neuronal damage, facilitate abnormal patterns of neural activity and precipitate

seizures. Future histopathological studies comparing implanted and non-implanted animals should thus be performed in order to establish whether hippocampal or parahippocampal lesions might facilitate epileptogenesis in these models. In a few occurrences, we recorded interictal spike-like activity in control animals after the implantation of depth electrodes, or even supradural ones (Ghestem and Bernard, unpublished). Although we cannot rule out the presence of such activity before the neurosurgical procedure, our hypothesis is that this activity stems from a neuro-inflammatory response.

The use of one of the two chemoconvulsants does not offer any advantage over the other when analyzing epileptiform activities during the latent period. Both kainic acid and pilocarpine are associated to the occurrence of spontaneous seizures after latent periods of similar duration. Interictal spikes recorded in temporal lobe regions also appear to show similar patterns of evolution over time. When performing histopathological studies on the latent period, the choice of either kainic acid or pilocarpine may however lead to different findings, since they are known to induce distinct neuropathological changes (see Section 5).

4. Chronic period

4.1. Seizure clustering

TLE patients often show clusters of seizures, during which seizures occur many times a day over multiple consecutive days (Haut, 2006). The kainic acid and pilocarpine models reproduce this feature of TLE, since in the first few days after injection epileptic animals alternate between seizure-free periods and periods of high seizure rates (Arida et al., 1999; Bortel et al., 2010; Cavalheiro, 1995; Drexel et al., 2012; Goffin et al., 2007; Grabenstatter et al., 2005; Lévesque et al., 2011; Mello et al., 1993; Williams et al., 2009). However, when animals are recorded over three months after a kainic acid-induced *status epilepticus*, the rate of occurrence of seizures, although in clusters, progressively increases over time (Williams et al., 2009). It was proposed that seizures clusters thus only obscure the exponential growth of seizure frequency (Williams et al., 2009). Such an increase of seizure frequency was also shown in the pilocarpine model during the first two months after status epilepticus (Arida et al., 1999).

4.2. Seizure onset patterns

Seizures during the chronic period in patients with TLE can be classified according to their onset pattern which, according to some studies, provides clues as to their origin and mechanisms of generation. The first type is the low-voltage fast onset pattern (LVF), characterized by a single sentinel spike followed by high-frequency activity (>25 Hz). The second type is the hypersynchronous onset pattern (HYP), which consists of seizures with multiple periodic spikes at onset, occurring at a frequency of approximately 2 Hz. LVF seizures often originate from hippocampal or extrahippocampal networks and patients showing these type of seizures have bilateral hippocampal atrophy (Ogren et al., 2009; Velasco et al., 2000). In patients with HYP seizures, the seizure onset zones are often located in focal hippocampal regions and they display unilateral hippocampal atrophy ipsilateral to the seizure onset zone (Ogren et al., 2009; Spencer et al., 1992; Velasco et al., 2000).

These findings have been reproduced in kainic acid-treated animals; to date, however, this has been reported only in animals in which kainic acid was topically injected in the hippocampus (Bragin et al., 1999, 2005). As in humans, onset zones of LVF seizures are diffuse whereas HYP seizures appear to originate from focal hippocampal or parahippocampal networks (Bragin et al., 1999, 2005). In the pilocarpine model, systemic injections also reproduce these two patterns of seizure onset during the chronic period (Lévesque et al., 2012; Toyoda et al., 2013). The prevalence of LVF and HYP seizures, however, may differ between epileptic patients and animals treated with chemoconvulsants. Indeed, the majority of epileptic patients show stereotyped patterns of seizure onset, that is either the LVF or the HYP pattern (Velasco et al., 2000), whereas epileptic animals alternate between LVF and HYP seizures (Bragin et al., 2005; Lévesque et al., 2012).

Studies performed in the pilocarpine model on these two onset patterns have shown that besides distinct onset zones, their mechanisms of generation may also differ. When analyzing high-frequency oscillations (HFOs, ripples: 80–200 Hz, fast ripples: 250–500 Hz) in these rats, LVF seizures are mostly associated to ripples whereas HYP seizures are often co-occurring with fast ripples (Lévesque et al., 2012). Such differences indicate that LVF seizures could be related to inhibitory processes with enhancement of interneuronal activity that will lead to synchronous GABA_A receptor-mediated signaling at seizure onset (Behr et al., 2014) since ripples are thought to represent population IPSPs generated by principal neurons entrained by synchronously active interneuron networks (Buzsáki and Chrobak, 1995; Ylinen et al., 1995). HYP seizures would, on the contrary, reflect the synchronous firing of principal glutamatergic cells since fast ripples have been associated to the synchronous in phase or out of phase firing of principal neurons (Behr et al., 2014; Bragin et al., 2011; Dzhala and Staley, 2003; Foffani et al., 2007; Ibarz et al., 2010). No studies in humans have so far confirmed these hypotheses.

4.3. Interictal spikes and high-frequency oscillations (80–500 Hz)

As in patients with TLE, epileptic animals show interictal spikes during the chronic period in both kainic acid (Chauvière et al., 2012; White et al., 2010; Zhang et al., 2011) and pilocarpine model (Bortel et al., 2010; Chauvière et al., 2012; Lévesque et al., 2011; Salami et al., 2014). In the kainic acid model, interictal spikes are, however, more likely to occur in animals that have experienced a convulsive SE, compared to controls and to animals that had a non-convulsive SE (White et al., 2010). Animals that experienced a convulsive SE are also more likely to show clusters of interictal spikes over widespread areas of the dentate gyrus (White et al., 2010). Interictal spikes may also occur in the subiculum, hippocampus and neocortex after the injection of kainic acid (Arida et al., 1999; Zhang et al., 2011). In the pilocarpine model, similar findings were obtained, since interictal spikes were also recorded in these regions during the chronic period in epileptic animals that experienced a convulsive *status epilepticus* (Bortel et al., 2010). The morphology and frequency of interictal spikes also change over time in this model; interictal spikes are shorter in duration in the hippocampus and occur at higher rates in the amygdala, compared to the latent period (Bortel et al., 2010). No study has, however, analyzed interictal spikes in pilocarpine-treated animals that showed a non-convulsive SE.

When analyzing HFOs, interictal spikes associated to fast ripples have been recorded in the subiculum of kainic acid-treated animals (Zhang et al., 2011). In the pilocarpine model, interictal spikes with fast ripples were also recorded in the subiculum, CA3 region of the hippocampus, entorhinal cortex and dentate gyrus (Lévesque et al., 2011). It was also reported that only in CA3, rates of interictal spikes with fast ripples correlate with seizure frequency (Lévesque et al., 2011). The analysis of type 1 and type 2 spikes and HFOs was also recently shown to change over time, since type 2 spikes associated to fast ripples increase in occurrence at the transition during the chronic period in CA3 (Salami et al., 2014).

The kainic acid and pilocarpine model thus induce similar patterns of ictal and interictal activity during the chronic period. Both models are also associated to the occurrence of clusters of seizures. The only main difference relating to the chronic period between the two models is the seizure frequency, since pilocarpine-treated animals show significantly higher seizure rates as compared to kainic acid-treated animals (Polli et al., 2014).

5. Neuropathological changes

The use of systemic administrations of kainic acid induces extensive neuronal damage in hippocampal and parahippocampal structures. Within 48 h after injection and mainly in animals that showed robust convulsions during *status epilepticus*, there is a loss of pyramidal cells in the CA1, CA3 and CA4 regions of the hippocampus (Ben-Ari et al., 1980; Cantallos and Routtenberg, 2000; Castro-Torres et al., 2014; Drexel et al., 2012; Haas et al., 2001; Heggli and Malthe-Sørenssen, 1982; Kar et al., 1997; MacGregor et al., 1996; Sloviter and Damiano, 1981; Sperk et al., 1983; Strain and Tasker, 1991; Suárez et al., 2012; Zhang et al., 2002). Animals surviving longer time periods (more than 48 h) after *status epilepticus* show neuron loss in the hilus and cell layer dispersion in the dentate gyrus, mossy fiber sprouting, shrinkage of nerve cells in the piriform and entorhinal cortices, olfactory bulb, substantia nigra, thalamus and mesencephalon (Ben-Ari et al., 1980; Buckmaster and Dudek, 1997; Covolan and Mello, 2000; Polli et al., 2014). Some studies have demonstrated that kainic acid-induced neuronal damage may however be strain-dependent (Cantallos and Routtenberg, 2000).

With the systemic administration of pilocarpine, cell damage is thought to first take place in dentate granule cells and hilus, followed by a neuronal degeneration in CA3 and CA1, between 24 h and 48 h after *status epilepticus* (Covolan and Mello, 2000). Several nuclei of the thalamus and the amygdala are also greatly damaged early after injection of pilocarpine (Clifford et al., 1987). Neuronal loss then extends to the subiculum, the septum, olfactory tubercle, amygdala, piriform and entorhinal cortices, neocortex and thalamus (Cavalheiro et al., 1996; De Guzman et al., 2006; Knopp et al., 2005; Turski et al., 1983). Mossy cells loss in the dentate hilus is observed only in epileptic animals and is thought to lead to mossy fiber sprouting and the generation of spontaneous seizures (Rose Priel et al., 1996). Recent evidence supports this hypothesis since the degree of mossy fiber sprouting is correlated with the frequency of spontaneous seizures (Shibley and Smith, 2002). However, a study by Buckmaster and Lew (2011) found in pilocarpine-treated mice that the suppression of mossy fiber sprouting before *status epilepticus* with the administration of rapamycin does not result

in a decrease in the frequency of spontaneous seizures, suggesting that it may only be an epiphenomenon without major epileptogenic effects. Therefore, both models reproduce the histopathological findings observed in human epilepsy, that is neuronal loss in the hippocampus and mossy fiber sprouting in the dentate gyrus, which are highly similar to those observed in the surgically resected hippocampi of patients with TLE (Sharma et al., 2007).

Both kainic acid and pilocarpine are associated to neuronal damage that first takes place in the hippocampus and that then progresses to extrahippocampal and extra-temporal networks, with approximately the same regions showing neuronal loss. It was however suggested that the main difference between the two models lies in the level of intensity and the time course of neuronal lesions. Systemic injections of pilocarpine are associated to high neuronal loss occurring after a short time interval compared to kainic acid for which neuronal loss is delayed (Covolan and Mello, 2000). For instance, Covolan and Mello (2000) reported that neuronal degeneration in temporal lobe regions is already visible within 3 h after a pilocarpine-induced SE whereas neuronal damage in the same regions following kainic acid can be seen only 8 h after the *status epilepticus*. These differences are thus likely to affect studies on the development of neuropathological alterations following *status epilepticus* and during the latent period. The high level of neuronal loss and its rapid progression may also explain the high mortality rate associated to pilocarpine.

6. Effect of anti-epileptic drugs on spontaneous seizures

In order to satisfy all the requirements for valid animal models of TLE, the initial *status epilepticus* induced by chemoconvulsants must be followed by the occurrence of spontaneous seizures that are refractory in most cases to pharmacological treatment. Some studies have been conducted on the effects of anti-epileptic drugs in kainic acid and pilocarpine-treated animals (White and Löscher, 2014). In the kainic acid model, some anti-epileptic drugs were proven effective when administered after the chemoconvulsant. For instance, a single intraperitoneal administration of topiramate or carbamazepine can reduce the frequency of spontaneous seizures but the anti-ictogenic effect is short-lasting (Grabenstatter et al., 2005, 2007). The daily oral administration of carbamazepine however appears more effective since its effect is long-lasting and may even completely block seizure occurrence (Ali et al., 2012; Grabenstatter et al., 2007). However, it is unclear if non-convulsive seizures are also blocked since no study has been performed so far on kainic-acid treated animals implanted with depth electrodes and treated with anti-epileptic drugs for multiple consecutive days. Also, since convulsive seizures tended to reoccur when the treatment was stopped in these animals, carbamazepine may only have an anti-convulsive effect.

In the pilocarpine model, the first study on the effect of anti-epileptic drugs was performed by Leite and Cavalheiro (1995), who showed that daily doses of phenobarbital, valproic acid, phenytoin and carbamazepine are effective in reducing the frequency of spontaneous seizures. Carbamazepine may also prevent hippocampal damage when administered early after *status epilepticus* (Chakir et al., 2006). A study by Glien et al. (2002) evaluated the effect of the novel anti-epileptic drug levetiracetam in pilocarpine-treated animals and

showed that seizure frequency is reduced in treated animals. The response to levetiracetam in these animals however varied from complete seizure control to no effect, despite plasma level concentrations in the same therapeutic range. We recently obtained similar results in pilocarpine-treated animals under levetiracetam: seizure frequency was significantly reduced in the first 15 days after status epilepticus compared to control animals (Lévesque et al., 2015).

Thus, both the kainic acid and pilocarpine animal models replicate the main features of the pharmacological treatment of the human condition since anti-epileptic drugs have significant anti-ictogenic properties, seizures tend to reoccur when the treatment is stopped and a subgroup of animals show pharmacoresistant seizures that are not even reduced in occurrence with anti-epileptic drugs. Therefore, these findings give support to the use of systemic chemoconvulsants as valid animal models of pharmacoresistant seizures that may help in the development of new therapeutical interventions.

7. Future challenges and impact for the development of new cures to epilepsy

Animal models are valuable tools to study TLE. They have contributed to the understanding of the pathophysiology of this disease, which is crucial for the development of effective therapeutic strategies for epileptic patients. The analysis of seizure onset zones and propagation pathways may help to perform better surgical interventions in refractory cases. Their use is also necessary in the pre-clinical discovery of anti-epileptic drugs and to evaluate the potential side effects and toxicity of pharmacological treatments. Finally, without animal models that allow the study of the development of an epileptic condition, from the initial brain insult to the occurrence of spontaneous seizures, it would be impossible to study the potential impact of anti-epileptic drugs on epileptogenesis.

We must, however, consider a few points that merit further investigation and thus represent new challenges for future studies. First, the gender, strain and age of animals affect the response to both kainic acid (Lévesque and Avoli, 2013; Zhang et al., 2008) and pilocarpine (Curia et al., 2008). This would not represent an important issue if similar types of methodologies were used in research protocols, but the use of rat, guinea pigs or mice of different ages complicate the interpretation of findings between laboratories. Second, although it is unclear why some epileptic patients do not respond to anti-epileptic drugs, the genetic, molecular or neurochemical causes of non-responder animals has also not been established in animal models of TLE. Third, it is difficult to evaluate with animal models the cause and consequences of the cognitive and behavioral alterations often observed in the human condition (Hui Yin et al., 2013).

8. Concluding remarks

We have reviewed evidence supporting the use of the kainic acid and pilocarpine animal models as valuable tools to understand the mechanisms underlying ictogenesis and epileptogenesis in TLE. Both models share similarities with the human condition regarding the initial brain insult and the electrographical and behavioral abnormalities associated to

recurrent pharmacoresistant seizures that occur after a latent period. However, compared to the human condition that is often associated with unilateral lesions (Engel, 1996), the systemic injection of chemoconvulsants induces extensive brain lesions, in extrahippocampal and often extratemporal regions. The significance of this effect is highly likely to be established in future studies, but recent evidence suggests that patients with TLE may also show neuronal damage outside of the hippocampus (Davis et al., 2002).

There is actually no animal model that reproduces all the features of the human condition. Non-human primate models are actually being developed in some laboratories and they appear to be associated to lesions highly similar to what is observed in humans (Perez-Mendes et al., 2011; Zini et al., 1993). More studies comparing the activity and physiological alterations in epileptic human and animal tissues are however needed in order to further establish the validity of these models. However, the question of homology may be meaningless. Patients with the exact semiology may have completely different anatomical alterations (e.g., hippocampal sclerosis vs. no overt anatomical modification) and be sensitive to very different AEDs (i.e., AEDs acting on different molecular targets). In other words, since there is not a specific type of TLE in patients, any experimental model is a good model as long as it is characterized by spontaneous seizures originating from temporal regions. One must not forget that seizures are latent activities; i.e., they are hardwired in “healthy” neuronal networks (any normal brain can seize if pushed hard enough). Although seizure dynamics may follow universal rules, there are multiple ways to get to seizure onset (Jirsa et al., 2014). This is highly reflected by the diversity of TLEs in patients and rodents.

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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.