The MTLE Mouse

Mesial Temporal Lobe Epilepsy Model

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The Mesial Temporal Lobe Epilepsy

The Mesial Temporal Lobe Epilepsy (MTLE) syndrome is characterized by the spontaneous recurrence of paroxysmal discharges in temporal lobe structures (hippocampus, amygdala, entorhinal and piriform cortex) that sometimes spread to cortical areas or thalamic nuclei (Wieser, 2004). This syndrome is associated with an hippocampal sclerosis which can be diagnosed on MRI (Cendes et al., 2002). The seizures are focal and are typically associated with an initial epigastric discomfort, followed by consciousness impairment, oroalimentary, gestural and verbal automatisms, and dystonic posturing of the arm contralateral to the epileptic discharge (Engel et al., 1996).

MTLE is often associated with an initial trauma like febrile convulsions in early childhood (Cendes et al., 2002). The "latent period" separating this initial trauma from the first epileptic episode, during which no clinical symptoms are observed, varies from several months to several years.

The resective tissue displays a pattern of hippocampal sclerosis characterized by cell loss in the CA1/CA3 areas and in the hilus of the hippocampus, along with gliosis and mossy fiber sprouting. A unique increase and dispersion of the granular cells of the dentate gyrus is also observed in most of MTLE patients and suggests an important reorganization of the hippocampal circuits (Mathern et al, 1997) (Houser et al, 1990).

MTLE generally become resistant to most antiepileptic drugs (AEDs) and surgical resection of the temporal lobe appears the most effective curative therapy (Engel et al., 1996; Ryvlin, 2003).

MTLE represents a major challenge in the clinical management of seizures (Semah et al., 1998 and 2004).
Several MTLE animal models were developed mainly in rat. These models are based on the anatomic and functional consequences of an initial status epilepticus induced by drugs or electrical stimulations (White, 2003). But those models don’t present every features of MTLE and are not resistant to AEDs.

Since several years a new model of MTLE has been developed in the mouse (Suzuki et al., 1995) which reproduces the behavioral, electrical, histological and pharmacological characteristics of human MTLE.

- **Epileptogenesis and Histological features**

In adult mice, unilateral injection of kainate (KA; 1 nmol) into the dorsal hippocampus results in a status epilepticus lasting several hours. It is associated with ipsilateral cellular loss in CA1, CA3 and hilus areas, gliosis and sprouting of mossy fibres. More particularly, a progressive dispersion and hypertrophy of the granule cells of the dentate gyrus is observed during the weeks that follow the injection of KA (Suzuki et al.,
1995; Bouilleret et al., 1999, Heinrich et al., 2006). These histological modifications are reminiscent of hippocampal sclerosis observed in MTLE patients.

Cell loses in CA1 and CA3 regions and dispersion of the granule cells of the dentate gyrus (DG) within the kainate injected side (Left: hippocampus control; right: injected hippocampus).

**Epileptogenesis and Electroencephalographic features**

In this model, we have shown the occurrence of spontaneous recurrent focal discharges which develop progressively during the 2-3 weeks post KA injection and then remain stable and stereotyped for the whole life of the animals (Riban et al., 2002). These seizures occur spontaneously, regularly (45 per hour) when the animals are in a state of quiet wakefulness and generally last 15 to 20 sec. They rarely spread to the cortex and are associated with behavioural arrest and/or mild motor automatisms.

Hippocampal (hippo) and cortical (cortex) EEG recordings of MTLE mouse showing focal hippocampal discharge
• **Pharmacological features**

One important feature of MTLE is the **resistance to most AEDs**. We showed that hippocampal discharges were suppressed in a dose-dependent way following **diazepam** administration (1, 2 and 3 mg/kg) in our MTLE mouse. However, suppression of seizures was observed with only high doses of **valproate** (400 mg/kg), **carbamazepine** (100 mg/kg) and **lamotrigine** (90 mg/kg), without dose-dependency and with side-effects. Moreover, studies have shown a lack of effect of phenytoin (*Riban et al.,* 2002) and levetiracetam (unpublished data) and aggravation was observed after a low dose of **lamotrigine** (30 mg/kg).

Our data show that besides benzodiazepines, only **pregabalin** significantly **suppresses hippocampal focal discharges in a dose-dependent way** (50 and 100 mg/kg) without side effects in the MTLE mouse.

These results show that hippocampal discharges in MTLE mice are resistant to most classic AEDs but not to a new antiepileptic drug, pregabalin.

Altogether, this model reproduces the behavioural, EEG and histological characteristics of human MTLE and presents the particularity to display dispersion of the dentate gyrus and focal hippocampal discharges resistant to most AEDs. Thus MTLE mouse constitutes a **validated tool for pharmacological evaluation of drugs for Mesial Temporal Lobe Epilepsy**.
The MTLE mouse
A model of Mesial Temporal Lobe Epilepsy

MTLE mouse fulfils most criteria for an efficient preclinical development of antiepileptic therapeutical strategies for MTLE:

**Construct validity (homology)**
- Initial status epilepticus
- Latent period
- Hippocampal sclerosis

**Face validity (similarity of symptoms)**
- Focal discharges
- Behavioral arrest and/or mild motor symptoms

**Predictivity (similarity of pharmacology)**
- Resistance to most classical AEDs
References


