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Research article

Isovaline attenuates generalized epileptiform activity in hippocampal and primary sensory cortices and seizure behavior in pilocarpine treated rats

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HIGHLIGHTS

- Isovaline attenuated hippocampal epileptiform activity in pilocarpine treated rats.
- Isovaline attenuated epileptiform activity in S1 cortex in pilocarpine treated rats.
- Isovaline attenuated behavioral generalized seizures in pilocarpine treated rats.

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ABSTRACT

Anti-seizure drugs are the most commonly employed treatment option for epilepsy and these generally provide effective management of seizures. However, 30% of patients with epilepsy are not adequately treated with anti-seizure medications and are considered intractable. Recently we reported that isovaline, a unique amino acid, could attenuate seizure like events (SLEs) in two *in vitro* hippocampal seizure models by selectively increasing the activity of interneurons, but not pyramidal neurons. Isovaline also attenuated hippocampal epileptiform activity and behavioral seizures *in vivo* in rats administered 4 aminopyridine (4AP). Here, we investigate whether isovaline is efficacious in attenuating secondarily generalized epileptiform activity and behavioral seizures in rats administered pilocarpine. We found that 150 mg/kg isovaline administered intravenously abolished pilocarpine-induced epileptiform activity in the primary sensory cortex and hippocampus and attenuated generalized forebrain behavioral seizures. We are the first to demonstrate that isovaline may be a plausible anti-seizure drug for secondarily generalized seizures and this could potentially lead to the development of a novel class of anti-seizure drugs focused around the unique mechanism(s) of isovaline.

1. Introduction

Epilepsy is a disease characterized by spontaneous recurrent seizures, which arise from synchronous and hyper excited neural networks. These seizures are generally managed with anti-seizure drugs although 30% of patients with epilepsy are unresponsive [5]. Therefore, there is considerable need to develop more effective anti-seizure drugs.

Recently, we investigated whether isovaline, a unique non proteinogenic amino acid that was first identified in the Murchison meteorite [4], had potential as a novel anti-seizure drug. While most proteinogenic amino acids are S enantiomers, isovaline has a racemic RS mixture [1]. Isovaline attenuated hippocampal seizure like events (SLEs) in brain slices bath perfused with low Mg^{2+}/high K^+ or 4 aminopyridine (4AP) [7]. It also attenuated hippocampal epileptiform activity and behavioral seizures in rats administered 4AP *in vivo* without causing sedation [9]. Although these findings suggest that isovaline has utility as an anti-seizure drug, the *in vivo* 4AP rodent model of epilepsy is not commonly employed in preclinical research nor does it represent a specific epileptic disorder. Here, we investigate whether isovaline can attenuate secondarily generalized epileptiform activity and behavioral seizures in rats administered pilocarpine. If so, we provide stronger support for isovaline's utility as an anti-seizure drug.

Abbreviations: AED, antiepileptic drug; SLE, seizure like event; 4AP, 4 aminopyridine; LFP, local field potential; eCoG, electrocorticogram; S1, primary sensory cortex.

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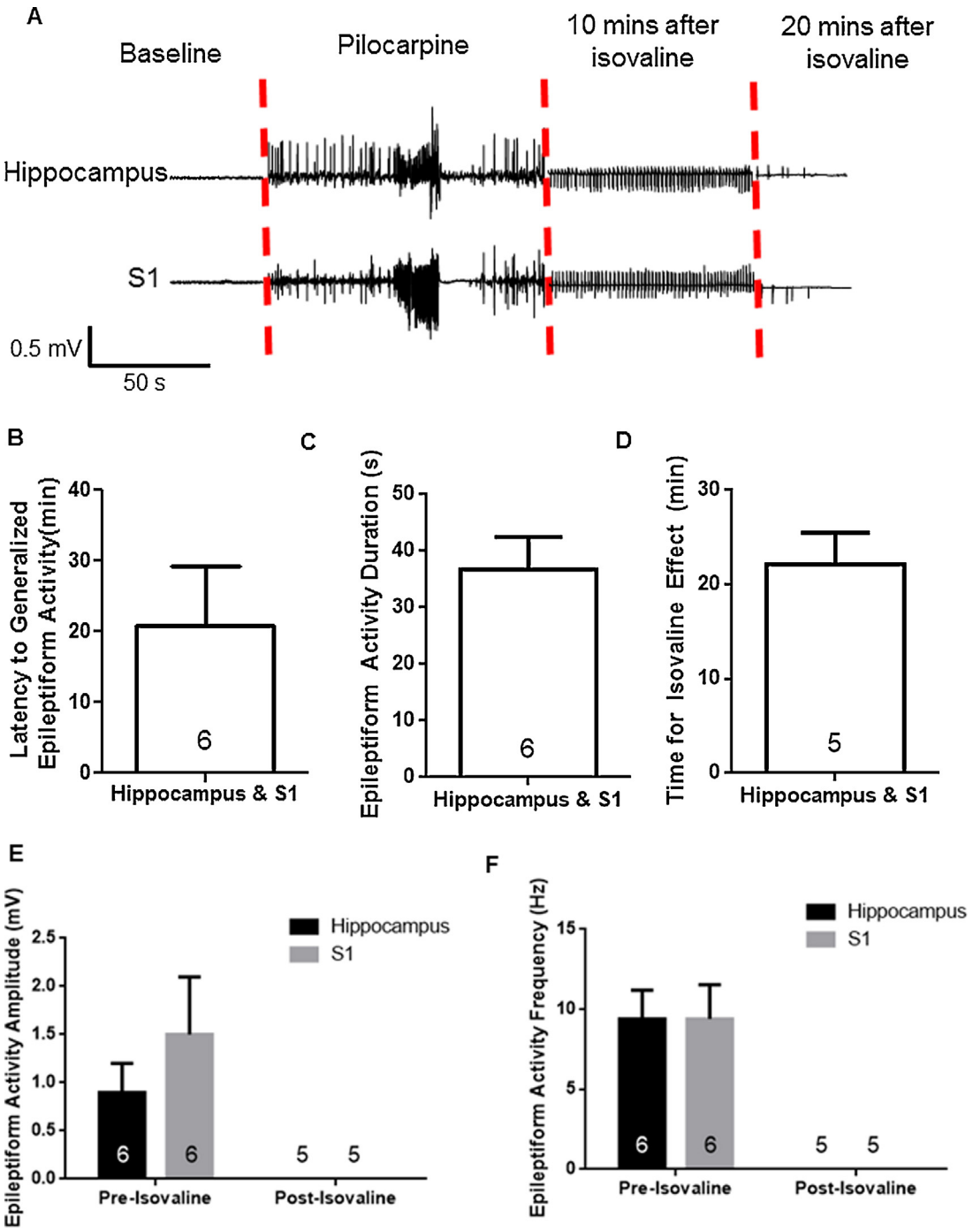

Fig. 1. (A) Isovaline abolished epileptiform activity in urethane anesthetized pilocarpine treated rats. Pilocarpine induced recurrent hippocampal and S1 epileptiform activity, which were abolished with 150 mg/kg. Traces within the vertical lines were spliced together and do not represent a continuous recording. Grouped data from 6 rats are represented as latency to first generalized epileptiform event (B), duration of epileptiform activity (C), epileptiform event amplitude (E) and frequency (F). Data from hippocampus and S1 are combined in (B)–(D) since epileptiform activity in each brain area is synchronized with each other. Numbers in histograms represent sample size and no data are shown for post-isovaline groups in (E) and (F) since epileptiform activity was abolished with isovaline. Since one rat died prior to isovaline injection, data for time for isovaline effect (D) is from 5 rats.

2. Materials and methods

2.1. Animals, surgery and electrophysiology

All procedures were performed on male Sprague Dawley rats (225–350 g) using approved protocols consistent with The Code of Ethics of the World Medical Association for experiments involving animals. Animals were housed in pairs in their home cage until testing was performed. Animals were exposed to a 12-h light/dark cycle (lights on at 7:00 AM). To record secondarily generalized epileptiform activity in anesthetized rats administered pilocarpine, we followed similar surgery procedures as before [9] and obtained local field potentials (LFPs) from recording electrodes in the left hippocampus and right primary sensory cortex (S1). In brief, rats were anesthetized with an intraperitoneal (IP) injection of 1.2 g/kg urethane and placed in a stereotaxic frame (David Kopf Instruments, CA, USA). Incision and craniotomy was performed and a stainless steel twisted wire (125 μm, Plastics One, VA, USA) was lowered into