Epilepsy & Behavior 79 (2018) 117–125

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Favorable adverse effect profile of brivaracetam vs levetiracetam in a preclinical model

Nathalie T. Sanon [a,1], Jonathan Gagné [a,b,1], Daniele C. Wolf [a,c], Soumia Aboulamer [a], Ciprian M. Bosoi [a], Alexe Simard [a], Estelle Messiet [a], Sébastien Desgent [a,c], Lionel Carmant [a,c,*]

[a] Centre de Recherche, Centre Hospitalier Universitaire CHU-Sainte-Justine, Québec, Canada
[b] Département de Sciences Biomédicales, Université de Montréal, Québec, Canada
[c] Département de Neurosciences, Faculté de Médecine, Université de Montréal, Québec, Canada

ARTICLE INFO

Article history:
Received 29 September 2017
Revised 15 November 2017
Accepted 19 November 2017
Available online xxxx

Keywords:
Social behavior
Brivaracetam
Levetiracetam
Temporal lobe epilepsy
Kainic Acid model

ABSTRACT

Levetiracetam (LEV), and its newer selective analog brivaracetam (BRV), are two seizure medications that share an innovative mechanism of action targeting the Synaptic Vesicle Protein 2A (SV2A), altering neurotransmitter release and decreasing seizure frequency. Behavioral changes are the most significant adverse effects reported by patients taking LEV. We hypothesize that BRV, the more potent SV2A analog, could exert less behavioral side effects, as it requires lower doses than LEV. Using Kainic Acid (KA)-treated and control rats, we measured adverse behavioral effect profiles of LEV, BRV, or Saline, on social and nonsocial behaviors. Our data indicate that both tested drugs had no effect on locomotion, anxiety levels, fear learning, depression-like behavior, and memory retention in rats. However, when considering social interactions, we first confirmed the epilepsy-induced strong increase in aggressive behaviors and specific hippocampal neuronal loss. We furthermore observed, in Sham rats, that LEV-treated animals were 2 times faster to attack at first encounter, had 5 times more aggressive behaviors, and had significantly less social behaviors than control rats. In all circumstances, BRV rats behaved like Saline rats, suggesting that BRV treatment in rats leads to significantly less aggressive behaviors than LEV treatment at the doses used, while there are limited differential effects between these two drugs on other types of behaviors. Since increased aggressiveness has been reported in patients well controlled on LEV, this study indicates based on our findings, that BRV could represent an effective alternative to LEV to limit aggressiveness problems due to this antiepileptic drug (AED) therapy.

1. Introduction

Keppra® (levetiracetam (LEV)) is an effective seizure medication often used as first intention among all drugs available on the market. However, multiple clinical reports have shown that some patients receiving Keppra® are more likely to have psychiatric adverse events, namely: anxiety, depression, hostility, and emotional lability [1]. Brivaracetam (BRV), the newest member of the "racetam" family, is a (4R)-propyl derivative selective Synaptic Vesicle Protein 2A (SV2A) analog of LEV. The BRV has a 10-fold greater ligand affinity for the SV2A than LEV and also inhibits sodium channels in a voltage-dependent manner [2]. There seems to be a correlation between SV2A binding affinity and anticonvulsant potency [3]. The BRV has been reported to be 6 to 12 times more potent than LEV in different animal models of seizure and myoclonic activity [4]. The BRV's broader anticonvulsant and favorable tolerability profiles as well as better potency in various animal models has translated into efficient doses nearing 10-fold lower than LEV in Phase II–III clinical trials [3,5]. However, the correlation between adverse effects in BRV and LEV is still uncertain, and the available experimental data on the topic are limited [6]. Thus, additional animal model studies are needed to clarify and better understand the behavioral changes associated with BRV as well as putative advantages of using BRV over LEV, in terms of adverse events. To do so, we used the widely accepted Kainic Acid (KA) model to mimic temporal lobe epilepsy (TLE) in rats, which induces spontaneous recurrent seizures and neuronal loss in the hippocampus [7], specifically in the Cornu Ammonis regions 1 and 3 (CA1 and CA3) areas. We, therefore, used this model to test LEV and BRV effects on the behavior of epileptic

Abbreviations: AED, antiepileptic drug; AMPA receptors, α-Amino-3-hydroxy-5-Méthylisoazol-4-Propionic Acid receptors; BRV, brivaracetam; CA1, CA3, Cornu Ammonis regions 1 and 3; CS, Conditioning Stimulus; EPM, Elevated Plus Maze; FC, Fear Conditioning; FS, Forced Swim; i.p. injection, intraperitoneal injection; KA, Kainic Acid; LEV, levetiracetam; MWM, Morris Water Maze; OF, Open Field; P60, postnatal day 60; RI, Resident-Intruder; SV2A, Synaptic Vesicle Protein 2A; SE, status epilepticus; TLE, temporal lobe epilepsy; US, Unconditioning Stimulus.

* Corresponding author at: Dr. Lionel Carmant Laboratory, Room 3.17.100_6, Centre de Recherche, CHU Ste-Justine, 3175 Côte-Ste-Catherine, Montréal, Québec H3T 1C5, Canada.
E-mail addresses: nathalie.sanon@umontreal.ca (N.T. Sanon), lionel.carmant@umontreal.ca (L. Carmant).

[1] These authors share coauthorship.

https://doi.org/10.1016/j.yebeh.2017.11.019
1525-5050/

and control rats. Thus, the goal of the present study was to determine if BRV caused less behavioral adverse effects than LEV at supratherapeutic doses, notably looking at exploration and learning capabilities, anxiety, depressive, social, and aggressive behaviors. Here, we show that LEV produced adverse effects mainly in social and aggressive behaviors, while the newer BRV did not, yielding similar behavioral effects as saline treatment.

2. Experimental procedures

Sprague–Dawley male rats (Charles River Laboratories; St. Constant, QC, Canada) were ordered at postnatal day 53 (P53), spent 1 week of accommodation in our animal facility being kept on a 12/12-hour light/dark cycle (lights on at 06:00) with food ad libitum (Teklad global rat food pellet 2014, Harlan). They were housed individually in their cage, with a square piece of cotton (3 × 3 cm) (Neslet, Ancare) and a PVC tube as enrichment. Cages were changed weekly, most of the times by the same animal care technician. All procedures for the use and care of animals followed the guidelines of the Canadian Council for Animal Care (CCAC), and the local committee Comité Institutionnel de Bonnes Pratiques Animales en Recherche (CIBPAR) approved the procedures (Protocol #479). In this respect, we considered the '3R' concept (Replacement, Reduction and Refinement) when planning the experiments.

2.1. KA and test drug injections

At postnatal day 60 (P60), the rats were separated in two groups and received a first intraperitoneal (i.p.) injection (1 ml/kg) of either KA (12 mg/kg) or a saline solution (0.9% NaCl) [8]. The KA injection induced status epilepticus (SE) starting about 1 h after injection and was permitted to last for a maximum of 2 h. At most 3 h after KA during stage 4–5 behavioral seizures [9], a dose of diazepam (2.5 mg/kg i.p.) was administered to stop KA-induced SE and limit mortality, while still allowing epileptogenesis (see Fig. 1 inset) [10]. Following KA injections and after SE, rats were given moistened food pellets over 2 days to prevent dehydration and for better recovery. All rats were then left to mature for 30 days (Fig. 1). In the long-term, KA provoked spontaneously occurring and recurrent seizures, consistent with the clinical diagnosis of epilepsy. Furthermore, the cellular modifications observed in the rat brain 1 month following SE are similar to those observed in patients with TLE, notably hippocampal sclerosis, characterized by neuronal loss, gliosis, and molecular changes in the hippocampus [11].

At P90, all rats received an injection (1 ml/kg, i.p.) of either: Saline solution (0.9% NaCl), LEV (300 mg/kg), or BRV (30 mg/kg) (LEV and BRV powders obtained from UCB, were diluted in saline), resulting in 6 different groups of treated rats: Sham-Saline/Sham-LEV/Sham-BRV/

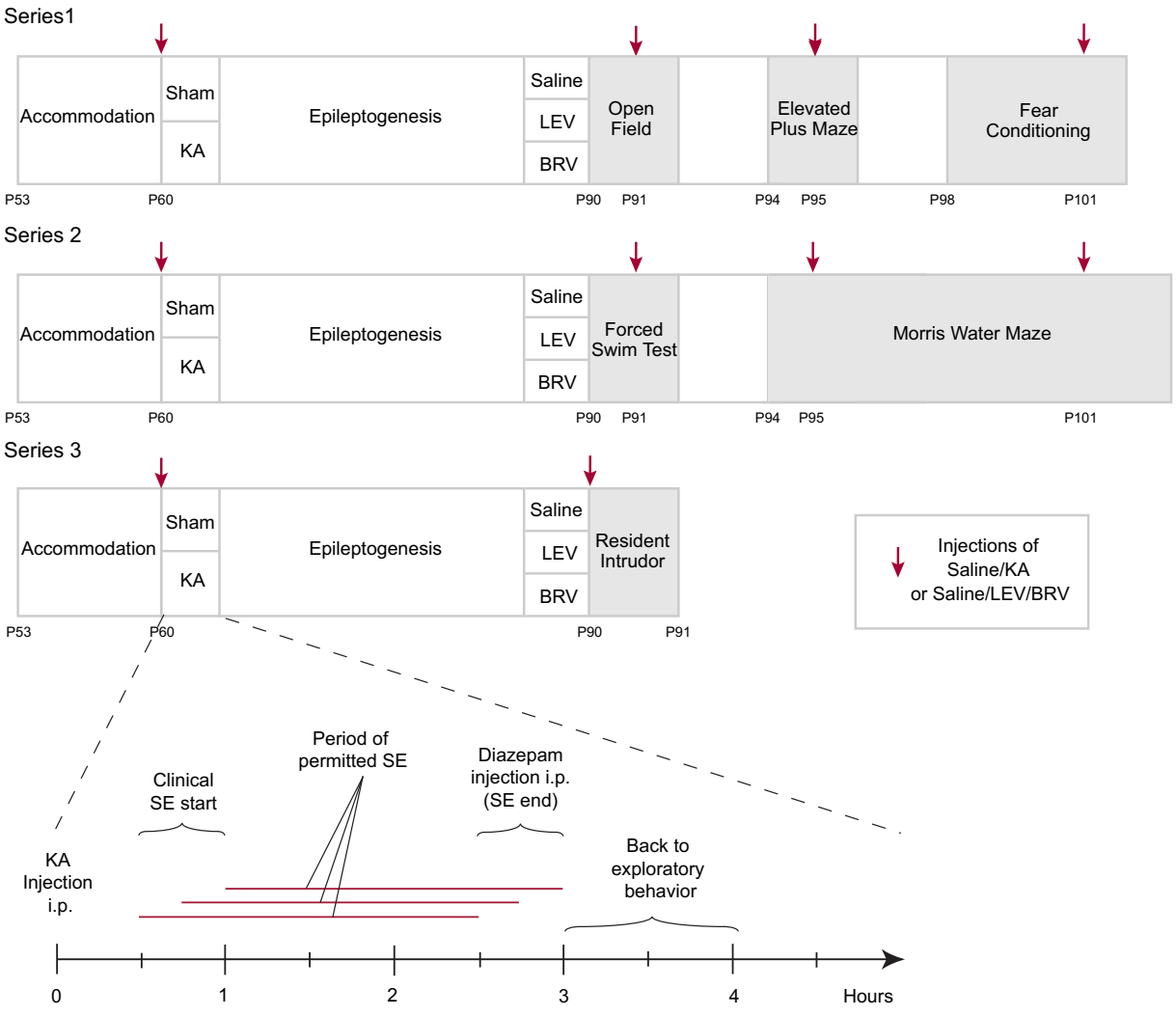

Fig. 1. Experimental timeline. Timeline of experimental conditions exhibiting use of rats, from their arrival (P53) to testing time (P90). Rats in Series 1 were submitted to the OF, EPM, and FC tests; rats in Series 2 were submitted to the FS and MWM tests; finally, rats in Series 3 were only submitted to the RI, test an extremely stressful and at times violent test. Red arrows indicate drug injections. Bottom timeline is an expansion of the KA and diazepam injection period at P60 and illustrates the approximate times of status epilepticus (SE), which vary from one animal to another. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)