Epilepsy & Behavior 87 (2018) 25–31

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Acute foot-shock stress decreased seizure susceptibility against pentylenetetrazole-induced seizures in mice: Interaction between endogenous opioids and cannabinoids

Armin Shirzadian [a,b,c], Sattar Ostadhadi [a,b,d,1], Mahsa Hassanipour [e,f], Hamed Shafaroodi [a,b], Mina Khoshnoodi [a,b], Arya Haj-Mirzaian [a,b], Mohammad Sharifzadeh [c], Shayan Amiri [g], Mehdi Ghasemi [h], Ahmad Reza Dehpour [a,b,d,*]

[a] Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[d] Brain and Spinal Cord Injury Research Center, Neurosciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[e] Physiology-Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[f] Department of Physiology and Pharmacology, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[g] Regenerative Medicine Program, Department of Biochemistry and Medical Genetics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada
[h] Department of Neurology, University of Massachusetts Medical School, Worcester, MA, 01655, USA

ARTICLE INFO

Article history:
Received 17 September 2017
Revised 18 June 2018
Accepted 20 June 2018
Available online xxxx

Keywords:
Seizure
Foot-shock stress
Opioids
Cannabinoids
Mice

ABSTRACT

Background: Stressful conditions affect the brain's neurotransmission and neural pathways that are involved in seizure susceptibility. Stress alters the intensity and/or frequency of seizures. Although evidence indicates that chronic stress exerts proconvulsant effects and acute stress has anticonvulsant properties, the underlying mechanisms which mediate these effects are not well understood. In the present study, we assessed the role of endogenous opioids, endocannabinoids, as well as functional interaction between opioid and cannabinoid systems in the anticonvulsant effects of acute foot-shock stress (FSS) against pentylenetetrazole (PTZ)-induced seizures in mice.

Methods: Prolonged intermittent FSS was chosen as an acute stress model. Seizure threshold was determined after 30 min of stress induction in male Naval Medical Research Institute (NMRI) mice (20–30 g). Opioid and cannabinoid receptor antagonists were administered before animal placement in the FSS apparatus.

Results: Acute FSS significantly decreased seizure susceptibility in animals. The administration of the cannabinoid receptor 1 (CB_1) antagonist, AM251, completely blocked the anticonvulsant effect of acute FSS at the doses of 1 pg/kg–100 μg/kg but not at 1 fg/kg. Pretreatment with the nonspecific opioid receptor antagonist, naltrexone (NTX), significantly inhibited the anticonvulsant effects of acute FSS at 1 and 2 mg/kg but not at 0.3 mg/kg. However, coadministration of the subeffective doses of AM251 (1 fg/kg) and NTX (0.3 mg/kg) reversed the anticonvulsant effects of acute FSS.

Conclusions: Opioid and cannabinoid systems are involved in the anticonvulsant effects of acute FSS, and these neurotransmission systems interact functionally in response to acute FSS.

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1. Introduction

Exposure to acute and chronic stress has many effects on brain activity and development and is able to alter seizure susceptibility in humans and animals [1]. Experiencing stressful events is associated with a variety of physiological, biochemical, and pathological changes in both peripheral organs and the central nervous system (CNS) and is considered as a risk factor for the development of neurological and psychiatric disorders [2–5]. Epilepsy is considered as one of the most common devastating neurological disorders and affects more than 50 million people worldwide [6]. Evidence indicates that stress level has a great impact on seizure susceptibility [7]. Based on the severity, duration, and nature of stressors, previous studies have reported that stressful events have different effects on seizures [8–10]. In experimental animal models, acute stressors (such as restraint stress, swim stress, cold-restraint stress, and foot-shock stress (FSS)) are known for their anticonvulsant properties while chronic stressors have been reported to increase seizure susceptibility [11–15]. There are several endogenous, neural, and endocrinological mechanisms that are involved in

* Corresponding author at: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box 13145–784, Tehran, Iran.
E-mail address: dehpoura@sina.tums.ac.ir (A.R. Dehpour).
[1] Unfortunately, this author passed away.

https://doi.org/10.1016/j.yebeh.2018.06.035
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anticonvulsant effects of acute stress. In this regard, gamma-aminobutyric acid (GABA)-ergic and noradrenergic neurotransmission, the hypothalamus–pituitary–adrenal (HPA) axis, the and opioid system have been reported to be involved in acute stress response [14,16]. Previous studies have revealed that acute stress is able to increase both expression and release of endogenous opioid peptides in CNS [17,18]. Morphine as a potent opioid receptor agonist exerts biphasic effects on seizure threshold. Our lab has shown that morphine at low doses has anticonvulsant effects whereas at relatively higher doses, it is proconvulsant in different animal models of seizure [16,19,20]. Further, it has been shown that the endogenous cannabinoid system contributes to stress response [21–25]. Moreover, exogenous cannabinoids affect seizure threshold by modulating excitatory and inhibitory neurotransmitters in the brain regions associated with epileptogenesis through cannabinoid type 1 (CB_1) receptors [26–32].

Opioid and cannabinoid systems are well known to have several functional interactions in both physiological and pathophysiological processes such as nociception, drug addiction, convulsion, hypothermia, immune regulation, anxiety, intestinal motility, and locomotion [33–36]. Several lines of research showed that exogenous cannabinoids induce release of endogenous opioid peptides and also suggested the same signal transduction pathways for these two important neurotransmission systems [37].

Based on this background, the primary aim of this study was to investigate the role of endogenous opioids and endocannabinoids in the anticonvulsant effects of acute FSS in mice. In addition, the possible interaction between opioid and cannabinoid systems in seizure threshold alterations in response to acute FSS was also investigated.

2. Materials and methods

2.1. Animals

Male Naval Medical Research Institute (NMRI) mice weighing 20–30 g were used in this study. The animals were kept in colony cages (4–6 mice in each cage) with free access to food and water under standardized conditions with a 12 h light–dark cycle and a controlled temperature (24 ± 1 °C). The animals were acclimatized to the experimental room before performing the experiments. All tests were conducted between 10:00 a.m. and 2:00 p.m. All procedures were in accordance with the institutional Guideline for the Care and Use of Laboratory Animals and were approved by the Tehran University Ethics Committee.

2.2. Chemicals

The following drugs were used throughout the study: AM251 (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide), a specific CB_1 receptor antagonist (Tocris, UK); naltrexone (NTX), a nonspecific opioid receptor antagonist, (Sigma, UK); and pentylenetetrazole (PTZ), a GABA receptor antagonist, (Sigma, UK). The NTX and PTZ were dissolved in sterile isotonic saline solution, but AM251 was prepared in DMSO. AM251 and NTX were administered intraperitoneally (i.p.) in a volume of 10 mL/kg of a mouse's body weight. The PTZ was administered intravenously (0.5%, i.v.) to perform seizure experiments.

2.3. Acute FSS

Acute stress was induced using a plexiglass box (30 × 30 × 40 cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter set 1 cm apart). Foot shock (3-mA scrambled shock stimulus, 50 Hz) was delivered through a scrambler to the grid floor. Animals were exposed to prolonged foot shock for 30 min (1-s pulses delivered every 5 s). The animals were acclimatized to the foot-shock apparatus for 25 min before stress induction. We injected saline (10 mL/kg) to the control mice and put them in the apparatus without any shock delivery for a specific time [38,39].

2.4. Seizure threshold assessment

An infusion pump (Harvard, USA) slowly infused PTZ (0.5%) at a constant rate of 1 mL/min into the lateral tail veins of unrestrained freely moving mice via a 30-gauge dental needle that was inserted into the mice's tails and secured by a narrow piece of adhesive tape. Infusion was stopped when forelimb clonus followed by full clonus of the mice body was observed. The minimum dose of PTZ (mg/kg of mouse weight) for induction of clonic seizure was measured as an index of seizure threshold. The threshold is dependent on the PTZ dose and time and is considered as a standard experimental method of clinical clonic seizures [40].

2.5. Treatments

According to our previously published study [11], prolonged and intermittent FSS was chosen as an established paradigm to exert anticonvulsant effects against PTZ-induced seizures. In the first experiment, the effects of acute FSS on the PTZ-induced seizure threshold were evaluated. Animals received 10-mL/kg saline before being placed for 30 min in the apparatus with or without FSS. Seizure threshold was determined 1, 15, 30, and 60 min after FSS termination. In the second experiment, the possible involvement of opioid or cannabinoid systems in the anticonvulsant effects of FSS was assessed. In this experiment, the PTZ-induced seizures were determined after treating animals with NTX (0.3, 1, and 2 mg/kg) 15 min before or AM251 (1 fg/kg, 1 pg/kg, 1 ng/kg, 1 μg/kg, 10 μg/kg, and 100 μg/kg) 30 min before they were placed in the apparatus with or without FSS. The third experiment was performed to assess the interaction between opioid and cannabinoid systems. The subeffective doses of NTX and AM251, which by themselves did not have any effect on the seizure threshold, were coinjected. Animals were treated with a combination of NTX (0.3 mg/kg) 15 min before and AM251 (1 fg/kg) 30 min before being placed in the apparatus with or without FSS.

2.6. Statistics

One-way analysis of variance (ANOVA) followed by Tukey multiple comparisons using GraphPad Prism software version 6 was used to analyze the data of clonic seizures. Data are expressed as mean ± S.E.M. $P < 0.05$ was considered the significance level between the groups.

3. Results

3.1. Effects of acute FSS on seizure threshold

As depicted in Fig. 1, prolonged FSS induced a significant increase in the seizure threshold in the PTZ model of clonic seizures. Fig. 1 also shows the time courses of the anticonvulsant effect of FSS in mice. Data have shown that the maximum anticonvulsant effect was manifested when tests were performed 1 min after stress induction and lasted for 30 min after the stress session. When the mice were tested 60 min after stress induction, no anticonvulsant effect was noticed.

3.2. Administration of AM251, a selective CB_1 receptor antagonist, abrogated the anticonvulsant effects of acute stress

The effect of AM251 administration on the seizure threshold is shown in Fig. 2. AM251 injection did not alter the seizure threshold in nonstressed animals in comparison with the saline-injected nonstressed group ($F(8, 36) = 0.1244$, $P > 0.05$, Fig. 2A). However, AM251 administration significantly reversed the stress-induced anticonvulsant effect. AM251 injection at the doses of 1 pg/kg ($P < 0.01$),

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