Pharmacology, Biochemistry and Behavior 158 (2017) 7–13

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Posterior hypothalamus glutamate infusion decreases pentylenetetrazol-induced seizures of male rats through hippocampal histamine increase

Atieh Arzhang, Mahmoud Elahdadi Salmani*, Taghi Lashkarbolouki, Iran Goudarzi

Faculty of Biology, Damghan University, Damghan, Iran

ARTICLE INFO

Keywords:
Orexin 2 receptor
Glutamate receptor
PTZ
Seizure
Posterior hypothalamus
Histamine

ABSTRACT

Objectives: Seizures are epileptic manifestations that are intrinsically modulated through different neurotransmitters and receptor systems. Although glutamate increases excitation and hence seizures, it activates other systems which could potentially terminate seizures. Histamine originates from neurons of the posterior hypothalamus (PH) and can mediate anticonvulsant properties, but the effect of local PH glutamate on hippocampal histamine content is unknown. Therefore, in this study, the effect of PH glutamate and the involvement of hippocampal histamine in pentylenetetrazol (PTZ) induced seizure activity was studied.

Materials and methods: OX2R antagonist (TCS OX2 29, 40 nmol/1 µl, intra-PH), AMPA/Kainate receptor antagonist (CNQX, 3 mM, intra-PH) and glutamate (1 mM) were injected bilaterally into PH using stereotaxic surgery. The intravenous PTZ infusion model was used to generate behavioral convulsions and the amount of hippocampal histamine content was then measured using a biochemical method.

Results: Administration of glutamate into PH decreased both seizure stage and the duration of tonic-clonic convulsion (TCC) with increasing TCC latency and hippocampal histamine content. Blocking OX2Rs alone or coinhibition of OX2Rs and AMPA/kainate receptors reversed these effects by increasing both seizure stage and TCC duration, and by decreasing both latency and consequent histamine content.

Conclusions: Our findings suggest that glutamate administration into PH may control seizures (stages and duration) through increasing the hippocampal histamine content.

1. Introduction

Seizures result from hyper-excitability in brain tissue (Hauser, 1975) that lasts a few minutes (Lado and Moshe, 2008) and typically self-terminate, involving glutamatergic (Casillas-Espinosa et al., 2012; John et al., 2008) and histaminergic neurotransmission (Kamei, 2001; Scherkl et al., 1991). Dysfunctional glutamate transmission is the main cause of long lasting seizures in the hippocampus and probably some pharmacoresistant seizures (Bialer and White, 2010), which take longer duration with the failure of physiological mechanisms responsible for seizure termination (Lado and Moshe, 2008).

The central histaminergic neurons are located in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (PH) projecting throughout the brain (Panula et al., 1989) to regulate excitability and control of cognition, appetite, arousal, and other brain functions (Haas et al., 2008). Researchers describe that the histaminergic system functional disturbance is associated with some pathologies like epilepsy (Haas et al., 2008; Kukko-Lukjanov et al., 2010). It is also shown that histaminergic neurons control different aspects of seizures such as the number of stimuli required for the onset and severity of seizures, and even the duration of ictal activity detected in the electroencephalogram (EEG) (Harada et al., 2004). Accordingly, studies suggest that the brain histamine system seems to be involved in regulating seizure susceptibility (Scherkl et al., 1991) and anticonvulsant action (Kamei, 2001; Paxinos, 2007; Scherkl et al., 1991; Yawata et al., 2004; Yokoyama et al., 1992). Furthermore, it has been reported that in histidinemic patients with higher histamine content in the brain, the rate of childhood convulsions is quite low (Yokoyama, 2001). Thus, the histaminergic system, which regulates the activity of many brain areas exhibits a potential anticonvulsant function and could be a promising target for the development of new anti-epileptic drugs (AEDs) (Kukko-Lukjanov et al., 2010).

Various afferents from different parts of the brain and mainly from the nucleus of the diagonal band of Broca (DBB), the lateral preoptic area (LPO), and the lateral hypothalamic area (LHA) have been identified to terminate in the TMN (Yang and Hatton, 1997). Most of the evoked responses from mentioned nuclei are fast GABAergic and the remaining (25%) are excitatory glutamatergic (Yang and Hatton,

Abbreviations: PTZ, pentylenetetrazol; OrxR, orexin receptor; PH, posterior hypothalamus; CSF, cerebro-spinal fluid

* Corresponding author at: School of Biology, Damghan University, Cheshme Ali Road, Damghan, Iran.
E-mail address: elahdadi@du.ac.ir (M. Elahdadi Salmani).

http://dx.doi.org/10.1016/j.pbb.2017.05.004
Received 20 December 2016; Received in revised form 5 May 2017; Accepted 6 May 2017
Available online 08 May 2017

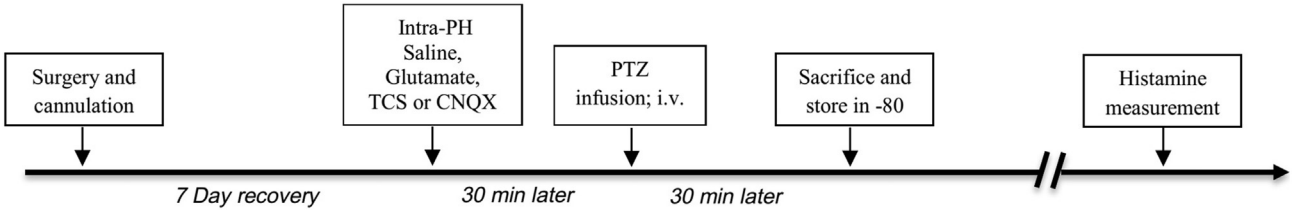

Fig. 1. Timeline of the experiments. After 7 day recovery from surgery and cannulation, intra-PH saline, glutamate, OX2R receptor antagonist (TCS), or AMPA/Kainate receptor antagonist (CNQX) was administered and PTZ was infused to induce convulsions, 30 min later. Following 30 min behavioral observations, the animals were sacrificed and then the extracted hippocampi were stored in − 80 freezers until histamine biochemical measurement.

1997). Immunochemical studies have identified reciprocal connections between orexin neurons of LHA and the PH histamine neurons. The same group also reported that LHA orexin neurons densely innervate TMN neurons where orexin receptor 2 (OX2R) is highly expressed (soma and dendrites) (Yamanaka et al., 2002). In addition, studies indicate that 90% of the orexin-ir terminals in the TMN release levels of glutamate (Torrealba et al., 2003). The orexin and glutamate released from the colocalized vesicles in axon terminals in the TMN depolarize PH histaminergic neurons and increase their firing rate via postsynaptic receptors (Eriksson et al., 2001; Torrealba et al., 2003). However, the glutamate applied in the LPO or LHA evoked both inhibitory and excitatory responses (Yang and Hatton, 1997) which may interfere with the orexinergic and glutamatergic receptor activation. Furthermore, application of NMDA (Okakura-Mochizuki et al., 1996) or stimulation of metabotropic glutamate receptors (mGluRs) type2 (Fell et al., 2010) has been also shown to suppress the histamine release in the limbic areas, while the role of AMPA receptors has not been yet explored. Some researchers believe that the rapid changes of glutamate turnover in the PH, representative of AMPA receptor activation, are linked to REM sleep/non-REM sleep cycle (John et al., 2008). Therefore, AMPA/Kainate receptor system may help to find the missing link between glutamate and orexin-induced excitability and histamine release. To this end, the present study investigates the effect of glutamate infusion into the PH on PTZ- induced convulsions and the involvement of the local OX2Rs and AMPA/Kainate glutamate receptors and their probable role in hippocampal histamine content.

2. Materials and methods

2.1. Animals

Male Wistar rats, weighing 200–220 g (young; 2.5 months old) purchased from Razi Institute (Karaj, Iran) were employed in this study. The rats were maintained on 12 h light: 12 h dark cycles in a room at 23 ± 2 °C for at least one week following arrival. Light periods started at 7:00 a.m. and rats were kept five per cage with access to food and water. All experiments were done in accordance with the National Institutes of Health Guide for the care and use of laboratory animals (NIH publication No. 29–80 revised 1996) and conformed to the research ethical standards for the care and use of animals at Damghan University. Additionally, care was taken to minimize the number of animals used in each experiment and their suffering.

2.2. Drugs

TCS OX2 29 (TCS for short; cat, 3371), CNQX (AMPA/Kainate receptor antagonist; cat, c127) from Tocris Bioscience, Glutamate (cat, 1.00292.0250) from Merck, and PTZ (cat, P6500) from Sigma-Aldrich were used in this study. All of the chemicals were dissolved in saline.

2.3. Experimental groups

Animals were allocated into five experimental groups:

1. Naïve control animals (comparison for histamine data, $n = 5$).
2. Intravenous PTZ- induced convulsion (Goudarzi et al., 2015) (control for behavioral convulsions; PTZ; $n = 10$).
3. Glutamate intra-PH infusion and PTZ infusion (Glu + PTZ; $n = 10$).
4. TCS plus glutamate intra-PH infusion and PTZ infusion (Glu + TCS + PTZ; $n = 20$). This group was designed to explore the involvement of orexin receptor 2 in the glutamate anticonvulsive function of PH.
5. CNQX (Kitamura et al., 2009) plus glutamate plus TCS intra-PH infusion and PTZ infusion (Glu + TCS + CNQX + PTZ; $n = 10$).

In all antagonist receiving groups, following seven-day recovery from stereotaxic surgery, saline, TCS, glutamate or CNQX (0.3 µl of volume) was injected into PH. Thirty minutes later, rats received PTZ to induce convulsions (Fig. 1).

2.4. Surgical preparation (cannula implantation)

Adult rats (from all groups) were implanted a brain cannula into PH for intracerebral injection seven days before the behavioral study. The PH was localized in accordance with the coordinates of Paxinos and Watson (Paxinos, 2007). Briefly, the rats were anesthetized with a mixture of ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), and their heads were shaved and placed in a stereotaxic apparatus (Stoelting instruments, USA). Body temperature was maintained using a towel pad. Under aseptic conditions, a burr hole was drilled aiming at PH (3.72 mm caudal to bregma, 0.1 mm lateral to midline bilaterally, 8.4 ventral to the skull). The PH then received a stainless steel guide cannula (23 gauge) fitted with a 1 mm longer infusion cannula (30 gauge). The guide cannula was hardened with dental acrylic cement and surgical screws. Tetracycline antibiotic ointment was then applied to skull skin incision to prevent infections. After seven day recovery from surgery effects, 0.3 µl of glutamate and/or antagonist drugs or saline was injected by a syringe pump (WPI instruments, USA) with a slow speed of 0.5 µl/min. The cannula remained about 3 min on the site for the drug to diffuse.

2.5. Seizure induction procedure

This rat model was based on previously established methods of our laboratory (Goudarzi et al., 2015) as a modification from the older one (Mandhane et al., 2007). Pentylenetetrazol (PTZ; 25 mg/ml, i.v.), dissolved in saline, was infused with a constant rate (0.5 ml/min) using the syringe pump connected with a polyethylene tube and heparinized needle via the tail lateral vein. Every rat was freely moving and behaviorally monitored for 20 min in a transparent Plexiglas box with ventilation holes in a blind manner. PTZ was infused through the tail lateral vein 30 min following intra-PH infusion of glutamate, OX2R antagonist, and/or AMPA/Kainate receptor antagonist. The infusion was terminated when the first myoclonic twitches appeared, thus decreasing mortality from non-stop infusion while allowing seizures to propagate. Convulsions were scored as follows; 0, no response: 1, ear and facial twitching; 2, convulsive waves through the body; 3, myoclonic jerks; 4, tonic-clonic convulsions, rearing; 5, generalized