Brain Research 1661 (2017) 1–14

Contents lists available at ScienceDirect

Brain Research

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

Research report

Endocannabinoid-dependent protection against kainic acid-induced long-term alteration of brain oscillations in guinea pigs

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ARTICLE INFO

Article history:
Received 30 August 2016
Received in revised form 2 February 2017
Accepted 3 February 2017
Available online 10 February 2017

Keywords:
AM404
URB597
Medial septum
Hippocampus
Entorhinal cortex
Amygdala

ABSTRACT

Changes in rhythmic activity can serve as early biomarkers of pathological alterations, but it remains unclear how different types of rhythmic activity are altered during neurodegenerative processes. Glutamatergic neurotoxicity, evoked by kainic acid (KA), causes hyperexcitation and acute seizures that result in delayed brain damage. We employed wide frequency range (0.1–300 Hz) local field potential recordings in guinea pigs to study the oscillatory activity of the hippocampus, entorhinal cortex, medial septum, and amygdala in healthy animals for three months after KA introduction. To clarify whether the activation of endocannabinoid (eCB) system can influence toxic KA action, AM404, an eCB reuptake inhibitor, and URB597, an inhibitor of fatty acid amide hydrolase, were applied. The cannabinoid CB1 receptor antagonist AM251 was also tested. Coadministration of AM404 or URB597 with KA reduced acute behavioral seizures, but electrographic seizures were still registered. During the three months following KA injection, various trends in the oscillatory activities were observed, including an increase in activity power at all frequency bands in the hippocampus and a progressive long-term decrease in the medial septum. In the KA- and KA/AM251-treated animals, disturbances of the oscillatory activities were accompanied by cell loss in the dorsal hippocampus and mossy fiber sprouting in the dentate gyrus. Injections of AM404 or URB597 softened alterations in electrical activity of the brain and prevented hippocampal neuron loss and synaptic reorganization. Our results demonstrate the protective potential of the eCB system during excitotoxic influences.

1. Introduction

Oscillations in rhythmic brain activity arise from the synchronized activity of neurons and are thought to play an essential role in information processing (Vinogradova, 1995; Buzsáki, 2006). Oscillation disturbances in vulnerable brain areas can serve as early indexes of pathological changes (Bragin et al., 2002; Salami et al., 2014; Dümpelmann et al., 2015). However, it remains unclear how different types of oscillations are altered during neurodegenerative processes.

Glutamatergic excitotoxicity is one of the factors leading to the development of neurodegeneration. It was discovered that an intra-brain injection of kainic acid (KA), a potent analog of glutamate, induces behavioral seizures and neuropathological lesions, which can be exploited in animal models of epilepsy (Ben-Ari et al., 1979). Unfortunately, seizure pathology often resists pharmacological therapy (Mazarati et al., 1998; Mayer et al., 2002). One of the prospective seizure-modifying approaches is activation of the endocannabinoid system as a natural homeostatic regulator (for review see Kano et al., 2009). This system includes the cannabinoid $G_{i/o}$-coupled (inhibition of adenylyl cyclase and Ca2+ channels, activation of K+ channels) CB1 and CB2 receptors, their endogenous ligands (endocannabinoids, hereafter referred to as eCBs), and the associated enzymes participating in synthesis, transport and degradation of these ligands. Synthesis of eCBs from membrane precursors is carried out "on demand" depending on current brain activity. Two known eCBs, anandamide and 2-arachidonoyl glycerol

Abbreviations: 2-AG, 2-arachidonoyl glycerol; BA, basal nucleus of the amygdala; eCBs, endocannabinoids; FAAH, fatty acid amide hydrolase; HFO, high frequency oscillations; KA, kainic acid; LFP, local field potential; MS, medial septum; SE, status epilepticus.

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http://dx.doi.org/10.1016/j.brainres.2017.02.003
0006-8993/

(2-AG) are greatly elevated in response to a variety of pathological events (Panikashvili et al., 2001; Marsicano et al., 2003; van der Stelt et al., 2006). eCBs mostly act as retrograde messengers and, upon their release from postsynaptic neurons, modulate neurotransmitter release via activation of presynaptic cannabinoid receptors (for review see Kano et al., 2009).

Despite the abundance of work clarifying the role of eCB in the regulation of acute seizures (Wallace et al., 2001, 2002, 2003; Shafaroodi et al., 2004; Karanian et al., 2005, 2007; Bahremand et al., 2008; Coomber et al., 2008; Naderi et al., 2008, 2011; Kozan et al., 2009; Mason and Cheer, 2009; Rizzo et al., 2009; Naidoo et al., 2011, 2012; Shubina and Kichigina, 2012; Citraro

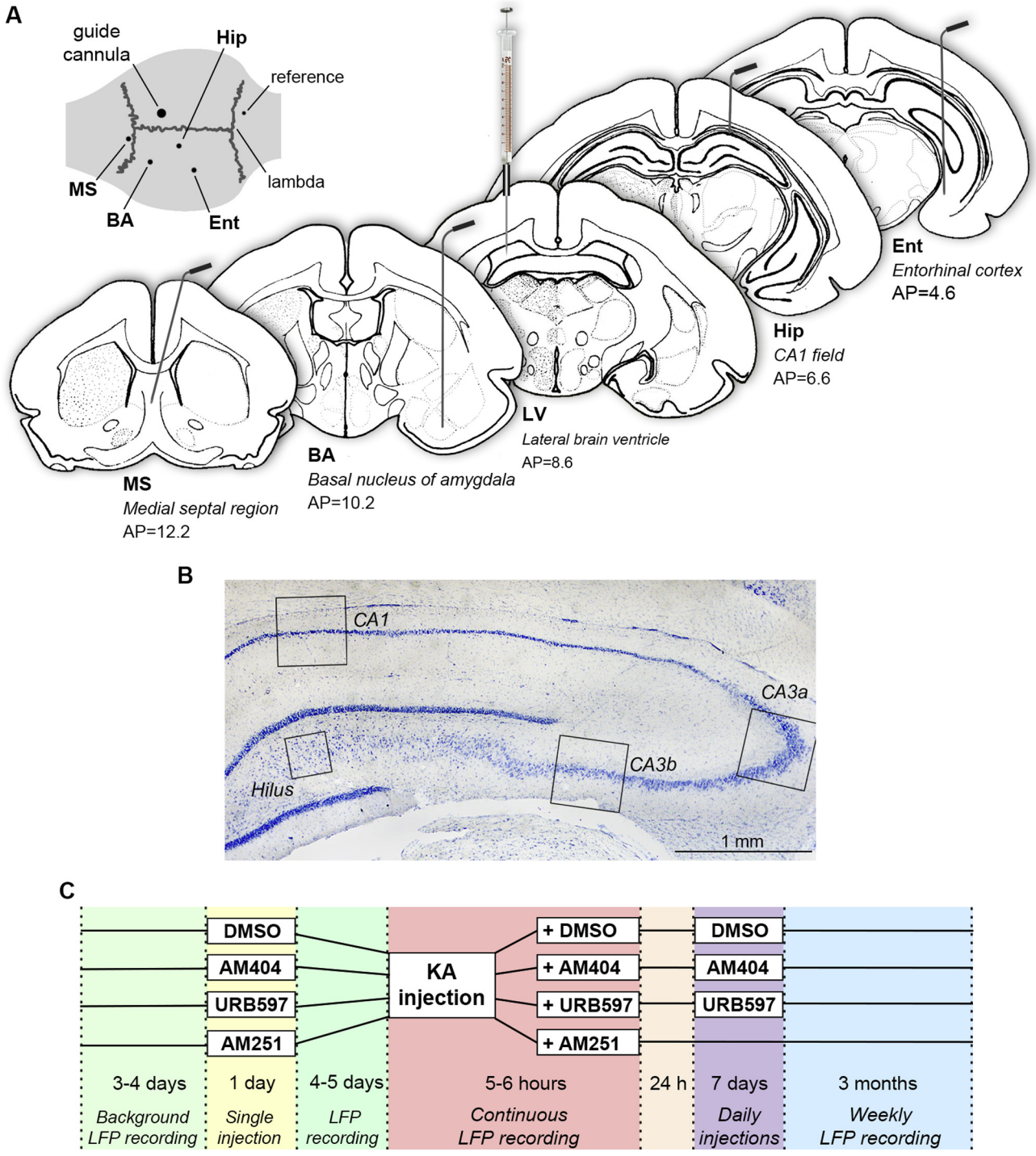

Fig. 1. Experimental design. (A) Scheme of electrode and guide cannula arrangement and their positioning according to Rapisarda and Bacchelli (1977). Recording electrodes were positioned in the medial septum (MS), basal nucleus of the amygdala (BA), CA1 field of the hippocampus (Hip) and entorhinal cortex (Ent), whereas the guide cannula for microinjections was implanted above the right lateral brain ventricle (LV) contralaterally to the recording electrodes. (B) Depiction of areas for neuronal quantification shown in the Nissl-stained coronal slice of dorsal hippocampus. Squares mark the counting frames in the CA1, CA3a, CA3b and hilus. (C) Schematic protocol of the experiment. Following the baseline LFP recordings and single injections of the substances used (DMSO, AM404, URB597 or AM251), KA was coadministered with vehicle (DMSO) or cannabinoid-related compounds (AM404, URB597 or AM251) and animals were continuously monitored for 5–6 h. After KA administration, daily injections of vehicle (DMSO) or cannabinoid-related compounds (AM404 or URB597) were made for 7 days and LFP recordings were performed weekly for 3 months.