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Research Paper

Target-specific alterations in the VIP inhibitory drive to hippocampal GABAergic cells after status epilepticus

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ABSTRACT

Status epilepticus (SE) is associated with complex reorganization of hippocampal circuits involving a significant loss of specific subtypes of GABAergic interneurons. While adaptive circuit plasticity may increase the chances for recruitment of surviving interneurons, the underlying mechanisms remain largely unknown. We studied the alterations in the inhibitory tone received by the hippocampal CA1 oriens/alveus (O/A) interneurons from the vasoactive intestinal peptide (VIP)- and calretinin (CR)-expressing interneurons using the pilocarpine-induced status epilepticus (SE) model of epilepsy. Our data showed that, while the overall density of the VIP/CR-co-expressing interneurons remained preserved, the number of axonal boutons made by these cells within the CA1 O/A was significantly lower after SE. Furthermore, VIP/CR interneurons exhibited significant alterations in their dendritic morphology and passive membrane properties. Subsequently, while all O/A interneuron types, including oriens-lacunosum moleculare (OLM), bistratified (Bis) and basket cells, exhibited decrease in spontaneous inhibitory drive, Bis and basket cells showed a smaller amplitude of light-evoked IPSCs mediated by the selective activation of VIP-positive interneurons. These data point to the target cell-specific changes in the inhibitory tone provided by the VIP cells to O/A interneurons following SE. Given that basket, Bis and OLM cells coordinate different subcellular domains of pyramidal neurons, significant disinhibition of basket and Bis cells along with a previously reported loss of the OLMs may result in a redistribution of inhibition converging onto pyramidal neurons, with a direct impact onto their recruitment to epileptiform network activity and seizure propagation.

1. Introduction

Altered GABAergic inhibition is a hallmark of most forms of epilepsy. Depending on the brain area and the specific inhibitory pathway, it may appear lessened or augmented but consistently modified in human patients and in animal models of epilepsy (Bernard et al., 2000; Chen et al., 1999; Mackenzie et al., 2016; Mann and Mody, 2008; Muldoon et al., 2015; Sloviter, 1991). One of the classic theories of epileptogenesis is based on the hypothesis that reduction of inhibition in neuronal networks is the cause of hyperexcitability that lead to the appearance of epileptiform activity (Avoli and de Curtis, 2011; Prince, 1968). In support of this viewpoint, studies showed that among the common anomalies observed during experimental temporal lobe epilepsy (TLE) in the hippocampus is the complex structural and functional reorganization of its inhibitory microcircuits, involving a selective loss of certain types of GABAergic interneurons (Avoli et al., 2005; Cossart et al., 2001; Dinocourt et al., 2003; Houser and Esclapez, 1996; Morin et al., 1998a, 1998b; Sloviter, 1987). On the other hand, the idea of the overall network hyperexcitability in epilepsy has been recently challenged as recordings from human epileptic patients and non-anesthetized epileptic mice point to rather sparse neuronal activity during epileptiform electrophysiological patterns (Keller et al., 2010; Muldoon et al., 2013, 2015; Sabolek et al., 2012; Trevelyan et al., 2015; Truccolo et al., 2011; Zhou et al., 2007). Moreover, during interictal spikes, synchronized hippocampal CA1 inhibition could lead to silencing of pyramidal cells, thus limiting the propagation of the epileptiform activity and creating conditions for functional deafferentation of downstream networks (Cohen et al., 2002; Muldoon et al., 2015; Schevon et al., 2009; Wozny et al., 2003). Taken together, these viewpoints indicate that alterations in GABAergic inhibition through changes in the connectivity and properties of GABAergic interneurons may play a critical role in the genesis and propagation of epileptiform activities.

GABAergic interneurons in the CA1 hippocampus comprise a highly diverse population of the local and long-range projecting inhibitory cells that coordinate the activity of pyramidal neurons in the brain-state dependent manner (Klausberger and Somogyi, 2008). In TLE, a selective loss of the CA1 interneurons, and more specifically the parvalbumin (PV) and somatostatin (SST)-expressing cells in the

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stratum oriens/alveus (O/A) is a well-described phenomenon (Dinocourt et al., 2003; Dam, 1980; Houser and Esclapez, 1996; Morin et al., 1998a, 1998b; Sanon et al., 2005; Sloviter, 1987). In particular, a vulnerable population of the SST O/A interneurons is formed by the oriens-lacunosum moleculare (OLM) cells, which decrease in number at the end of the second week after induction of status epilepticus (SE) in experimental animals (Cossart et al., 2001; Morin et al., 1998b). While a fraction of O/A interneurons is lost, the surviving cells change their connectivity and activity patterns (Chen et al., 2001; Cossart et al., 2001; Marchionni and Maccaferri, 2009; Peng et al., 2013), thus resulting in the appearance of pathological inhibitory dynamics.

Several factors, including the microcircuit connectivity and changes in the intrinsic and synaptic excitability of cells through extensive remodeling of intrinsic and synaptic conductances, can explain alterations in activity of interneurons after SE (Bernard et al., 2000; Biagini et al., 2013; Chen et al., 2001; Perez et al., 1996, 2006; Topolnik and Lacaille, 2009). Among these factors, the changes in the inhibitory coordination of hippocampal interneurons (Chamberland and Topolnik, 2012) have received little attention (Ma and Prince, 2012; Yu et al., 2015, 2016). Intriguingly, highly specialized populations of the calretinin (CR) and/or vasoactive intestinal peptide (VIP)-containing interneurons that make synapses selectively onto GABAergic cells exist in the hippocampus (Acsady et al., 1996a, 1996b; Chamberland et al., 2010; Gulyas et al., 1996; Tyan et al., 2014). In particular, the type 3 interneuron-specific (IS3) cells that co-express CR and VIP (Acsady et al., 1996b) and innervate different types of O/A interneurons coordinate their rhythmic recruitment (Tyan et al., 2014). While the CR-containing interneurons are vulnerable, both in animal epilepsy models and in human patients (Tóth and Maglóczky, 2014), the loss and morphological impairment of these cells depend on the TLE type and severity. For example, in the non-sclerotic hippocampus, the CR-positive interneurons are preserved but their dendrites exhibit substantial abnormalities (Tóth et al., 2010; Tóth and Maglóczky, 2014), pointing to possible functional aberrations. Furthermore, the CR-expressing interneurons form a heterogeneous population of cells (Gulyas et al., 1996); however, it is currently unknown which CR interneuron subtypes are lost and which may survive after SE, thus contributing to pathological inhibitory patterns. In this study, we addressed this question by focusing on VIP and CR-expressing cells in the mouse pilocarpine model of SE. Using a combination of immunohistochemistry, electrophysiological patch-clamp recordings and optogenetics in hippocampal slices, we found that the number of synapses formed by the VIP/CR-co-expressing interneurons, including IS3 cells, onto O/A interneurons is decreased after SE, resulting in the significant but cell type-specific disinhibition of O/A interneurons.

2. Methods

2.1. Animals

Male and female adult (P40-90) C57Bl6, VIP:Cre (Viptm1(cre)Zjh/J) (The Jackson Lab) and VIP-Channelrhodopsine2 (ChR2) mice obtained by crossing of the Ai32 (B6;129S-Gt(ROSA)26Sortm32(CAG-COP4*H134R/EYFP)Hze/J) with VIP:Cre mice were used in this study. Mice were housed in standard conditions (12 h/12 h light/dark cycle with the light on at 07:00, one per cage, with water and food *ad libitum*). All experiments were performed in accordance with the guidelines of the Animal Protection Committee of Laval University and the Canadian Council on Animal Care.

2.2. Pilocarpine mouse model of SE

The status epilepticus (SE) was induced in mice (18.5–22.5 g) by i.p. injection of pilocarpine (315–320 mg/kg; Sigma, St Louis, MO) as previously described (Curia et al., 2008; Turski et al., 1983). Briefly, scopolamine methyl nitrate (1 mg/kg; Sigma, St Louis, MO) was administered 30 min before pilocarpine to prevent the peripheric cholinergic effects. The animals of the experimental group received a single injection of pilocarpine dissolved in the sterile saline solution (0,9% NaCl). Control mice (sham) received a similar injection of scopolamine and, after 30 min, an injection of saline. After the pilocarpine administration, mice were replaced in their home cage and monitored during 2 h for seizure manifestation. The severity and duration of the acute epileptic seizures was determined using Racine scale (Racine, 1972). Following this period, an injection of diazepam (5 mg/kg; Sandoz) was used to terminate SE. All electrophysiological experiments and immunohistochemical analyses were performed between 27 and 50 days post-SE.

2.3. Slice preparation

Transverse hippocampal slices (300 μm) were prepared from the pilocarpine- (post-SE) and saline-injected mice 4–5 weeks after the injection as described (Camiré and Topolnik, 2014). Briefly, mice were perfused intracardially with the ice-cold sucrose-based solution containing in mM: 2 KCl, 1.25 NaH_2PO_4, 7 $MgSO_4$, 26 $NaHCO_3$, 10 glucose, 250 sucrose, 0.5 $CaCl_2$. Slices were cut using a vibratome (Microm, Thermofisher) in the same sucrose-based solution oxygenated with 95%O_2/5%CO_2, and transferred into the heated (35–37 °C) and oxygenated recovery solution containing in mM: 124 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 3 $MgSO_4$, 1 $CaCl_2$ and 10 glucose, in which they were left to recover for at least 1 h.

2.4. Electrophysiological patch-clamp recordings

For electrophysiological recordings, slices were transferred to the recording chamber perfused continuously (2 mL/min) with an artificial cerebrospinal solution (ACSF; in mM): 124 NaCl, 2.5 KCl, 1.25 NaH2PO4, 26 $NaHCO_3$, 2 $MgSO_4$, 2 $CaCl_2$ and 10 glucose (pH 7.3, oxygenated with 95%O_2/5%CO_2) and maintained close to the physiological temperature (32 ± 1 °C). The interneurons of interest within the hippocampal CA1 O/A were visually identified with an infrared CCD camera (IR1000, Dage) installed on the up-right fluorescence microscope (Zeiss Axioscope; Nikon Eclipse FN1), which was equipped with a 40× water-immersion objective (NA, 0.8). The patch pipettes (3.5–6 MΩ) were made from the borosilicate glass capillaries using a Flaming/Brown micropipette puller (Sutter Instrument Co.). For miniature inhibitory postsynaptic currents (mIPSCs) and spontaneous IPSCs (sIPSCs), whole-cell patch-clamp recordings were performed in voltage-clamp at 0 mV using the intracellular solution containing (in mM): 130 $CsMeSO_4$, 5 CsCl, 2 $MgCl_2$, 10 phosphocreatine, 10 HEPES, 0.5 EGTA, 4 ATP-TRIS, 0.4 GTP-TRIS, 0.3% biocytine (pH 7.2–7.3; 280–290 mOsm/L). mIPSCs were recorded in the presence of tetrodotoxin (TTX; 1 μM; Alomone Labs). Both mIPSCs and sIPSCs were recorded at 0 mV. For recordings of membrane properties of IS3 cells, current-clamp recordings were obtained using a K^+-based intracellular solution containing (in mM): 130 $KMeSO_4$, 5 KCl, 2 $MgCl_2$, 10 phosphocreatine, 10 HEPES, 0.5 EGTA, 4 ATP-TRIS, 0.4 GTP-TRIS, 0.3% biocytine (pH 7.2–7.3; 280–290 mOsm/L). The cell membrane properties were measured within the first minute of the whole-cell configuration. The acquisition of the data (filtered at 2–3 kHz and digitized at 10 kHz) was performed using the Multiclamp 700B amplifier and the Clampex 10.5 software (Molecular Devices, CA, USA). The series resistance (Rser; 5–25 MΩ) was constantly monitored during the experiment by applying a hyperpolarization pulse of 5 mV at the end of every recorded sweep. When Rser changed >15% the recordings were interrupted.

2.5. ChR2-based photostimulation

The activation of VIP interneurons that expressed the channelrhodopsin 2 (ChR2) was achieved through wide-field stimulation with blue light (two pulses of 5 ms each with a 50-ms interval)