Neuroscience 304 (2015) 190–197

ALTERED INHIBITION IN THE HIPPOCAMPAL NEURAL NETWORKS AFTER SPREADING DEPRESSION

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Abstract—Prolonged neuronal depression after spreading depression (SD) is followed by a late cellular and synaptic hyperexcitability. Intra- and extracellular recordings of bioelectrical activities were performed in the rodent hippocampus to investigate the role of γ-aminobutyric acid (GABA)-mediated inhibition in the late hyperexcitable state of SD. The effect of KCl-induced negative DC potential shifts was investigated on extracellularly recorded paired-pulse depression (PPD) and bicuculline-induced afterdischarges as well as intracellularly recorded inhibitory post synaptic potentials (IPSPs) in the hippocampal CA1 area. The results revealed that SD decreased the degree of PPD, enhanced the number and duration of bicuculline-induced afterdischarges, and reduced the amplitude and duration of IPSPs. Application of low concentrations of bicuculline before the induction of SD enhanced the inhibitory effect of SD on IPSPs. Data indicate the contribution of GABA-mediated inhibition to SD-induced delayed hyperexcitability. Modulation of GABA function in the late hyperexcitability phase of SD may play a role in therapeutic management of SD-related neurological disorders. **© 2015 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: spreading depolarization, epilepsy, migraine, stroke, hippocampus, disinhibition.

INTRODUCTION

Spreading depression (SD) is associated with self-propagating depolarization of neurons and glial cells in the cerebral neocortex, subcortical brain structures, and retina at the rate of 3–5 mm/min (Leao, 1944; Hansen and Zeuthen, 1981; Gorji, 2001). The onset of SD is accompanied by a brief period of neuronal excitation, which is immediately followed by a prolonged inhibition of neuronal activity and then (after 10–30 min) by a late cellular and synaptic hyperexcitability (Footitt and Newberry, 1998; Berger et al., 2008; Ghadiri et al., 2012).

The role of excitatory neurotransmitters in SD is widely investigated (Van Harreveld, 1959). Conversion of glutamic acid, released during SD, into γ-aminobutyric acid (GABA) has been suggested as the possible mechanism of hyperpolarizing type of inhibition at the late phase of unit activity blockade after SD (Krnjević et al., 1966; Phillis and Ochs, 1971; Bures et al., 1974; Ghaemi et al., 2014). Application of GABA caused a blockade of the SD penetration to the cortical island formed by subpial incision (Ochs and Hunt, 1960) as well as the SD propagation in the isolated chicken retina (Van Harreveld and Fifkova, 1971). It has been reported that $GABA_A$ currents were activated during the early phase of negative DC deflection (1–2 s prior to SD) and then were transiently suppressed one minute after the peak of SD (Aiba and Shuttleworth, 2014), which may contribute to early phase of excitability after SD.

Changes in cortical and subcortical excitability observed during the late hyperexcitability phase of SD have been suggested to contribute to the pathophysiology of some neurological disorders, such as migraine (Ghadiri et al., 2012) and epilepsy (Dreier et al., 2012). Partial disinhibition of $GABA_A$ receptors (induced by the application of low concentration of a $GABA_A$ blocker) has been shown to generate spiking activity during the late excitability state of SD in epileptic human brain tissues (Dreier et al., 2012) and in non-epileptic rat brain (Eickhoff et al., 2012). GABA neurotransmission, although not directly involved in the initiation and propagation of SD, plays a crucial role in maintaining the excitation of the neuronal networks, and interruption of GABAergic input may strengthen the late excitatory period following the depression phase of SD (Eickhoff et al., 2012). Altered neuronal and synaptic functions can be seen remote from the SD propagation in the neocortex (Martens-Mantai et al., 2014). Neocortical SD, both indirectly via the effect on input of the entorhinal cortex to the hippocampus or directly by propagation to the

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Abbreviations: SD, spreading depression; PPD, paired-pulse depression; IPSPs, inhibitory post synaptic potentials; ACSF, artificial cerebrospinal fluid.

http://dx.doi.org/10.1016/j.neuroscience.2015.07.035
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hippocampal structure, affects the hippocampal functions (Wernsmann et al., 2006). The contribution of GABAergic neurotransmission to the neuronal activities in the late hyperexcitable phase of SD in the hippocampus remains to be elucidated. The purpose of the present study was to determine the role of GABA-mediated inhibition in modulation of neuronal excitability in the late hyperexcitability phase of SD.

EXPERIMENTAL PROCEDURES

Slice preparation

All experiments were conducted in accordance to the guiding principles for the care and use of animals in the University of Münster, Germany (50.0835.2.0/A-18/2006). Adult Wistar rats (male, 300–350 g; 10–12 week old) were rapidly decapitated under deep isoflurane anesthesia and the brains were transferred to 4 °C artificial cerebrospinal fluid (ACSF) with 95% O_2 – 5% CO_2. After removing of the cerebellum and dividing the two cerebral hemispheres, the hippocampus and cortex were dissected and then sliced in a nearly horizontal plane (500 μm) with a vibroslicer (Campden Instruments, Lafayette, USA). The composition of ACSF was (in mmol/l) NaCl, 124; KCl, 4; $CaCl_2$, 1.0; NaH_2PO_4, 1.24; $MgSO_4$, 1.3; $NaHCO_3$, 26; and glucose, 10 (pH 7.4). ACSF was gassed with 95% O_2 and 5% CO_2 for 1 h. For prevention of cell injury during the preparation, concentration of $CaCl_2$ in the storage solution was increased to 2.0 mM after 30 min of incubation. Slices were individually transferred to an interface recording chamber, placed on a transparent membrane, illuminated from above and continuously perfused (1.5–2 ml/min) with carbogenated ACSF at 32 °C. To assure the oxygen supply, a warmed and humidified gas mixture of 95% O_2 and 5% CO_2 was evaporated over the surface of the slices.

Electrophysiological recordings

Extracellular recordings were obtained using a custom-made differential amplifier (Gorji et al., 2002) and intracellular recordings were performed by an active bridge mode amplifier (Gorji et al., 2011; filter 10 kHz). Extracellular DC potential recordings in the somatosensory neocortex and the hippocampal CA1 region were obtained with glass microelectrodes (150 mmol/l NaCl, 2–5 mΩ). Intracellular recordings were made from CA1 pyramidal neurons with sharp microelectrodes, which were filled with 2 mol/l potassium methylsulfate (50–90 mΩ). A constant positive or negative current was injected into the cells to set the membrane potentials to −40 mV or to −75 mV, respectively. The reference electrode and the connection to the microelectrode were symmetric Ag–Ag–Cl bridges. Intracellular current pulses were passed via an active bridge circuit and bridge balance was monitored and adjusted during recordings. Intracellular recording data acceptable for inclusion in the study met the following criteria: recording stability without any sign of injury discharges, membrane potential more negative than −45 mV with deviation less than 5% during the control period (Ghadiri et al., 2012). Using the bipolar extracellular stimulating electrodes placed in the alveus of CA1 region, inhibitory post synaptic potentials (IPSPs) were evoked in CA1 pyramidal cells. The distance between recording and stimulation electrodes was 350–500 μm (Masukawa and Prince, 1982). Extracellular field-evoked potentials were evoked by single pulses of electrical stimulation applied through a bipolar platinum electrode attached to the Schaffer collaterals of the hippocampus (0.5 ms duration, ∼0.5 mA). The results were digitized by a Digidata 1200 (Axon Instruments, Sunnyvale, CA, USA) and the data were collected and analyzed by Axoscope 10 (Axon Instruments, CA, USA). For intracellular recording, the amplitude (mV) and duration (ms) of IPSPs were measured.

Paired-pulse depression (PPD) paradigm

A bipolar electrode was positioned in the Schaffer Collaterals pathway and extracellular recordings were performed in the CA1 stratum pyramidale. Paired pulses were applied at inter-pulse intervals of 120 ms (0.5-ms duration, 0.3–0.6 mA). A 120-ms inter-pulse interval has been used to induce a light inhibition and prevent overlapping of traces. PPD is expressed as a percentage change in the peak amplitude for the second stimulation response versus the initial response.

Induction of SD

SD was triggered by injection of 3 M KCl through a glass electrode fixed in a special holder and connected with plastic tube to a home-made pressure injector. The tip of the electrode was inserted into the temporal cortex (layers I–II). An amount of KCl sufficient to induce SD was applied via high-pressure pulse (tip diameter, 2 μm; injection pressure, 0.5–1.0 bar applied for 200–300 ms, two separate injections, 1–3 nl per pulse, 2–5 mm apart from nearby recording electrodes). In control experiments, the same amount of ACSF was applied (Kazemi et al., 2012).

Bicuculline was purchased from Santa Cruz (Heidelberg, Germany) and was added by the perfusion solution. The solution was made up by dissolving the drugs in ACSF at the desired concentrations.

Statistical analysis

All data are given as mean ± SEM. The data were statistically analyzed by the Mann–Whitney rank sum test. Multiple comparisons were performed using analysis of variance test (ANOVA) for repeated measures followed by a Duncan's test. Significance was established when the probability values were below 0.05.

RESULTS

Induction of SD

After focal administration of KCl, extracellular potential recordings of the neocortex showed a transient slightly positive DC deflection, sometimes followed by a brief burst of spikes that heralded the appearance of the

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