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SYNAPTIC PLASTICITY-RELATED NEURAL OSCILLATIONS ON HIPPOCAMPUS–PREFRONTAL CORTEX PATHWAY IN DEPRESSION

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Abstract—It is believed that phase synchronization facilitates neural communication and neural plasticity throughout the hippocampal–cortical network, and further supports cognition and memory. The pathway from the ventral hippocampus to the medial prefrontal cortex (mPFC) is thought to play a significant role in emotional memory processing. Therefore, the information transmission on the pathway was hypothesized to be disrupted in the depressive state, which could be related to its impaired synaptic plasticity. In this study, local field potentials (LFPs) from both ventral CA1 (vCA1) and mPFC were recorded in both normal and chronic unpredictable stress (CUS) model rats under urethane anesthesia. LFPs of all rats were recorded before and after the long-term potentiation (LTP) induced on the vCA1–mPFC pathway in order to figure out the correlation of oscillatory synchronization of LFPs and synaptic plasticity. Our results showed the vCA1-to-mPFC unidirectional phase coupling of the theta rhythm, rather than the power of either region, was significantly enhanced by LTP induction, with less enhancement in the CUS model rats compared to that in the normal rats. In addition, theta phase coupling was positively correlated with synaptic plasticity on vCA1–mPFC pathway. Moreover, the theta-slow gamma phase–amplitude coupling in vCA1 was long-term enhanced after high frequency stimulation. These results suggest that the impaired synaptic plasticity in vCA1–mPFC pathway could be reflected by the attenuated theta phase coupling and theta–gamma cross frequency coupling of LFPs in the depression state.

Key words: ventral hippocampus, medial prefrontal cortex, theta rhythm, gamma oscillations, depression.

INTRODUCTION

Neural oscillations in the central nervous system provide a mechanism for the coordination between cognitive functions and neuron activities in multiple brain regions. Theta rhythm (3–8 Hz) is one of the most intriguing neural oscillations, which is dominant in several brain areas, especially in the rodent hippocampus (Buzsaki, 2002; Young, 2011). Additionally, gamma rhythms (30–100 Hz) have received particular attention, because of their strong relationship to higher brain functions (Csicsvari et al., 2003; Buzsaki and Wang, 2012). A growing amount of investigations support an idea that rhythmic synchronization, such as phase synchronization and unidirectional coupling of theta and gamma rhythms between different brain regions, plays a crucial role in neural communication and neural plasticity to promote learning and memory (Axmacher et al., 2006; Fell and Axmacher, 2011; Belluscio et al., 2012). However, it could be impaired in psychiatric disorders indicating the underlying cognitive dysfunction (Adhikari et al., 2010; Dzirasa et al., 2011).

As one of the most prevalent mental diseases, depression disorder is commonly caused by repeated exposure to an array of chronic stressors over a sustained period of time. Accordingly, the chronic unpredictable stress (CUS) model has been widely used as a traditional rodent model of depression. Multiple lines of evidence showed that cognition and memory were impaired in depression (Quan et al., 2011a; Millan et al., 2012), in which the inhibited synaptic plasticity in its target brain region, medial prefrontal cortex (mPFC), was believed to be an important cellular mechanism (Cerqueira et al., 2007; Quan et al., 2011a; Marsden, 2012). Since mPFC receives strong monosynaptic inputs from the ventral hippocampal CA1 (vCA1) (Thierry et al., 2000), besides of the synaptic transmission on this circuit, the increased rhythmic synchrony between the hippocampus and mPFC with cognitive demands is well established (Gordon, 2011). In freely behaving rats, positive correlation was found between the theta power of the vCA1 and mPFC, which was also associated with anxiety (Adhikari et al., 2010). Our previous studies indicated that theta phase coupling between the thalamus and mPFC correlated with LTP on the thalamocortical pathway in the depressive state (Zhang et al., 2011; Zheng et al., 2011, 2012; Zheng and Zhang, 2013). Consequently, one of the purposes of the study was to investigate the

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Abbreviations: CUS, chronic unpredictable stress; EMA, evolution map approach; HFS, high-frequency stimulation; LFPs, local field potentials; LTP, long-term potentiation; mPFC, medial prefrontal cortex; PAC-MI, phase–amplitude coupling-modulation index; PLV, phase- locking value.

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association between synaptic plasticity and phase coupling of neural oscillations, and explore how it was changed in depression.

In the current study, the CUS rat-model was established to simulate the depression-like state. The long-term potentiation (LTP) was induced on ventral hippocampal CA1 to the mPFC pathway in order to measure the strength of synaptic plasticity. The local field potentials (LFPs) were collected before and after the LTP induction, respectively. All the electrophysiological recordings were performed under the anesthetic state. Our main purpose was to investigate how neural oscillations were involved in synaptic plasticity by phase synchronization and phase coupling of theta and gamma rhythms between vCA1 and mPFC in the CUS rats. Furthermore, gamma oscillations in the dorsal hippocampus are believed to be split into distinct fast gamma (60–100-Hz) and slow gamma (30–60-Hz) subtypes that differentially route separate streams of information (Colgin et al., 2009; Colgin and Moser, 2010; Bieri et al., 2014). However, little was known about the slow and fast gamma in the vCA1. In the present study, the theta–gamma cross frequency coupling was measured in the vCA1 for both slow and fast gamma, respectively. The purpose of the analysis was to examine how the slow and fast gamma differentially changed in the CUS rats. And the relationship between theta–gamma cross frequency coupling and synaptic plasticity was addressed as well.

EXPERIMENTAL PROCEDURES

Subjects and CUS procedure

Male Wistar rats (27 rats, 250–350 g body weight) were housed on a 12-h light/dark cycle (lights on at 7 AM), and reared in standard rodent cages under the condition of a constant temperature (24 ± 2 °C). Food and water were supplied regularly during all phases of the experiment, except for the establishment of the CUS model. Thirteen rats were randomly selected to consist of the CUS group, in which the CUS procedure was performed for 21 days according to the modification method of Willner (1997). Seven kinds of stressors, including tail pinch, ice water swimming, reversed light/-dark cycle, cage tilt, water deprivation, noise stimulus and hot water swimming, were applied in apparently random order and at changeable times in a day, with each stressor performed once a week. Details of the experimental schedule for the CUS procedure could be found in our previous paper (Quan et al., 2011a). The normal rats were left intact throughout the modeling period. All procedures were in accordance with the guidelines of the Beijing Laboratory Animal Center, and approved by the Ethics Commission at the Nankai University. Every effort was made to minimize animal suffering and the number of animals.

Experimental design

Two lines of experimental protocols are presented in Fig. 1. In Protocol-A (Fig. 1A), two groups of rats were included, which were the control group (Con, $n = 8$) and the depression model group (Dep, $n = 7$). LFPs were collected for 20 min before the LTP induction, which was noted by 'pre-LTP LFPs'. And then the LTP was induced on the vCA1–mPFC pathway for 60 min (see next section for the details of LTP). Another 20-min LFP was recorded following the LTP induction, defined as 'post-LTP LFPs'.

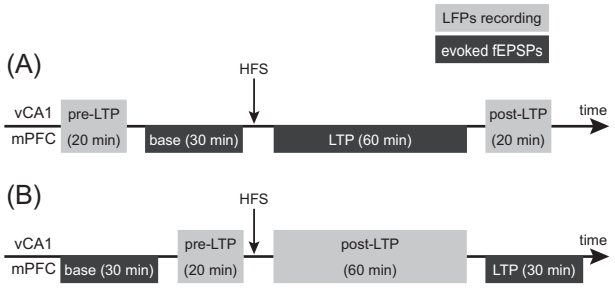

Fig. 1. Experimental designs for the Con and Dep groups. (A) In Protocol-A, two 20-min periods of LFPs were recorded before and after LTP induction, respectively. LTP on vCA1–mPFC pathway was induced for 60 min. (B) In Protocol-B, the LFPs were recorded right before and after the high-frequency stimulus. Evoked fEPSPs were recorded for 30 min after the LFP recordings. All the protocols are presented in detail in 'Experimental procedures' section.

In Protocol-B (Fig. 1B), LFPs recording and LTP induction procedures were basically reversed from those in the Protocol-A. During the experiments, 12 rats were divided into two groups, which were the Con ($n = 6$) and Dep ($n = 6$) groups. After the baseline collecting of evoked field excitatory postsynaptic potentials (fEPSPs) for 30 min, the LFPs were recorded for 20 min right before the high-frequency stimulation (HFS), noted as 'pre-LTP LFPs'. As soon as neural activities were stable over time after the HFS was triggered, the signals of 'post-LTP LFPs' were continuously recorded for 60 min, followed by 30-min evoked fEPSPs recorded in mPFC.

Surgical procedure and electrophysiology

The rats were anesthetized with 30% urethane (3.5 ml/kg, i.p., Sigma–Aldrich) and fixed on a stereotaxic frame (Narishige). Two small holes were drilled in the skull to allow the electrodes impartment in the brain. A concentric bipolar stainless steel electrode was lowered into the ventral part of the hippocampal CA1 (Fig. 3A; AP −6.3 to −6.5; L 5.5; H 4.0–5.0). A monopolar extracellular stainless steel recording electrode was placed into the prelimbic area (PrL) of mPFC (Fig. 3A; AP 3.0–3.3; L 0.7–1.0; H 2.8–3.4). The stereotaxic coordinates were derived from Paxinos and Watson (2006). The ground and reference electrodes were placed over the two hemispheres of the cerebellum symmetrically. The LFP signals were sampled simultaneously in both vCA1 and mPFC regions at 1-kHz sample frequency. For the LTP induction in the mPFC by stimulation of the vCA1 region, the test stimuli were delivered to the vCA1 region every 1 min at an intensity that evoked fEPSP of 70% of its maximum (range 0.2–0.5 mA). Baseline fEPSPs were recorded for 30 min, followed by two series of 10 HFS (250-Hz, 250-μs duration, 50 trains) at 0.1 Hz delivered at the same stimulus intensity as the test stimuli (Sui