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Research report

Reduced local field potential power in the medial prefrontal cortex by noxious stimuli

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ABSTRACT

Nociceptive signals produced by noxious stimuli at the periphery reach the brain through ascending pathways. These signals are processed by various brain areas and lead to activity changes in those areas. The medial prefrontal cortex (mPFC) is involved in higher cognitive functions and emotional processing. It receives projections from brain areas involved in nociception. In this study, we investigated how nociceptive input from the periphery changes the local field potential (LFP) activity in the mPFC. Three different types of noxious stimuli were applied to the hind paw contralateral to the LFP recording site. They were transcutaneous electrical stimulations, mechanical stimuli and a chemical stimulus (formalin injection). High intensity transcutaneous stimulations (10 V to 50 V) and noxious mechanical stimulus (pinch) significantly reduced the LFP power during the stimulating period ($p < 0.05$), but not the low intensity subcutaneous stimulations (0.1 V to 5 V) and other innocuous mechanical stimuli (brush and pressure). More frequency bands were inhibited with increased intensity of transcutaneous electrical stimulation, and almost all frequency bands were inhibited by stimulations at or higher than 30 v. Pinch significantly reduced the power for beta band and formalin injection significantly reduced the power of alpha and beta band. Our data demonstrated the noxious stimuli-induced reduction of LFP power in the mPFC, which indicates the active processing of nociceptive information by the mPFC.

1. Introduction

Noxious stimuli activate peripheral nociceptors to produce nociceptive signals (Dubin and Patapoutian, 2010) which are then transmitted to the spinal cord, the thalamus, and many other cortical and subcortical areas through ascending pathways (Basbaum and Jessell, 2000). Nociceptive signals are processed and encoded at various levels along these pathways. Once nociceptive signals reach the brain, they are processed in different brain areas to subserve different aspects of the pain experience. It is well accepted that the sensory discriminative properties of pain are encoded in the somatosensory cortex, and the affective and motivational component associated with pain is processed in the anterior cingulate cortex (ACC) and insular cortex (IC) (Price, 2000; Rainville et al., 1997; Treede et al., 1999; Zhang, 2006). These areas showed consistent activation in response to nociceptive input (Casey et al., 1994; Coghill et al., 1994, 2014; Derbyshire et al., 1997; Hsieh et al., 1996; Iadarola et al., 1998; Jones et al., 1991; Talbot et al., 1991). Other possible areas are involved in the affective-motivational aspect of pain are mediodorsal thalamus, amygdala, nucleus accumbens, and certain prefrontal cortical areas (Cardoso-Cruz et al., 2013; Neugebauer et al., 2009; Rainville, 2002).

Prefrontal cortex has started to gain attention in recent years for its role in pain processing (Apkarian et al., 2005; Neugebauer et al., 2009; Ochsner et al., 2006; Tracey and Mantyh, 2007). Decreased grey matter in prefrontal cortex has been associated with chronic pain in patients (Apkarian et al., 2004; Obermann et al., 2009; Seminowicz et al., 2011), which is suggested to be due to neurodegeneration and possible cell death. Contradictory results also exist in human imaging studies (Neugebauer et al., 2009). Both hypoactivity (Gündel et al., 2008; Jones and Derbyshire, 1997) and hyperactivity (Casey et al., 1996; Derbyshire et al., 1999; Lorenz and Casey, 2005; Lorenz et al., 2002) in the prefrontal cortex (PFC) in response to painful stimuli have been observed. This discrepancy may be due to different pain conditions, methodological

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variations (Derbyshire et al., 1997), as well as different subdivisions in the prefrontal cortex. The medial prefrontal cortex (mPFC), as one part of the prefrontal cortex, constitutes the major portion of the medial wall of the hemisphere and is anterior and dorsal to the genu of corpus callosum (Hoover and Vertes, 2007). It is involved in diverse functions, mostly in higher cognitive functions, such as memory, decision making and selective attention (Vertes, 2006). Morphological changes of mPFC to neuropathic pain (Metz et al., 2009) and decreased single cell activities to induced arthritis (Ji and Neugebauer, 2011) were observed in animals. The mPFC has four divisions: the medial agranular (AGm), anterior cingulate (AC), prelimbic (PL), and infralimbic (IL) cortices (Hoover and Vertes, 2007). PL is functionally homologus to the dorsal lateral prefrontal cortex (DLPFC) in human and nonhuman primates, because of their similar roles in cognition (Sylvie and Bruno, 2000). DLPFC of primates has beem proposed to been implicated in the cognitive aspect of pain (Wiech et al., 2008). Therefore, the study of pain processing in the PL of rodents can shed light on the pain processing in the DLPFC of primates. We tested the hypothesis that PL is actively involved in pain processing by measuring the local field potential (LFP) in the PL in response to different modailities of noxious input. LFP is the integrated extracellular electric activity in a small neuronal volume containing action potentials, synaptic potentials, and other membrane potential-derived fluctuations (Buzsáki et al., 2012). To our knowledge, this is the first study that examines the LFP property of mPFC in response to different noxious modalities.

2. Methods and materials

Six-month-old male Sprague-Dawley rats were used in this study and maintained at constant temperature and humidity under light-dark cycles of 12 × 12 h, with ad libitum access to food and water. All procedures were approved by the Institutional Animal Care and Use Committees of University of Texas at Arlington and followed the guidelines for the treatment of animals of the International Association for the Study of Pain (Zimmermann, 1983).

2.1. Animal preparation

Rats were anesthetized using sodium pentobarbital (50 mg/kg i.p.). The depth of anesthesia was confirmed by the absence of the withdrawal responses to tail pinch and toe pinch. A second i.p. injection was applied if needed. Continuous administration of anesthesia was accomplished by a catheter placed in the jugular vein (5 mg/ml pentobarbital at a rate of 1.0 ml/h, i.v.). Tracheotomy was performed in case artificial ventilation was needed. The rat was placed on a stereotaxic frame in a prone position. The temperature was kept at 37 °C with a feedback controlled heating blanket.

2.2. LFP recording

A burr hole was drilled on the skull to expose the brain surface above the target area. An electrode (Plastics One MS 303-1-B-SPC ELECT SS 2C TW .010in) was inserted in the right PL (3–3.7 mm rostral to the bregma, 0.5–0.8 mm lateral to the midline, 3–3.5 mm below the dura membrane). The electrode was connected to our custom-designed wireless LFP recorder which sent back the LFP signals to the receiver that was connected with the computer. The LFP signals were recorded by the Labview-based software on the computer. This wireless LFP recording system is based on the design by Zuo et al. (2012).

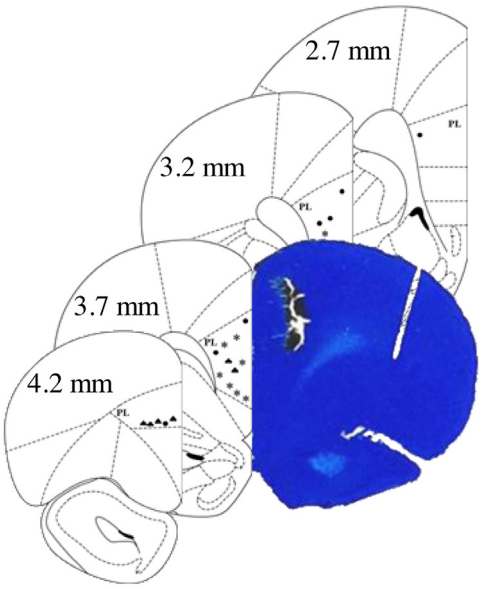

Fig. 1. Histology results. Schematic representation of the placement of electrode tips on coronal sections anterior to the bregma from 4.2 mm to 2.7 mm. Only those electrodes' tips in or within the borders of PL were included in the data analyses and shown here. A blue representative histological section at anterior 3.7 mm to bregma is presented in the middle. Asterisk: HIS group; black dots: group of mechanical stimuli and formalin injection; solid triangle: group of LIS and saline injection. PL: prelimbic area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
(Figure adapted from Paxinos & Waston (1998)

2.3. Noxious stimuli

Three different types of noxious stimuli were applied in left paw contralateral to the recording site in this study, transcutaneous electrical stimulation, mechanical stimuli, and formalin injection. The customized recording program was used to manually deliver a marker at the beginning and at the end of each stimulation. These markers showed up in a different synchronized parallel channel to the LFP recording channel, and were used as our time stamps for data analysis.

2.3.1. Transcutaneous electrical stimulation

Two groups were included in this experiment, the low-intensity group (LI, n = 6) and high-intensity group (HI, n = 8). Two curved stainless needle electrodes penetrated transcutaneously through the left ankle area and were spaced 1 cm apart. The location of the two needle electrodes and distance between them were kept consistent for each rat. The needle electrodes were connected to the Grass stimulator (Model S88; Grass Technologies, West Warwick, RI) to deliver the electrical stimulation. Stimulation parameters were frequency of 100 Hz, pulse width of 1 ms for 10 s at low intensities of 0.1, 0.5, 1, 2.5, 5 V for the LI group and high intensities of 10, 20, 30, 40, 50 V for the HI group. The inter-stimulation interval was 1 min in each group.

2.3.2. Mechanical stimuli

In this experiment (n = 7), graded mechanical stimuli were applied to the plantar surface of the left hind paw in the order of brush, pressure and pinch. Brush was applied by a small camel hair brush; pressure and pinch were applied by a venous bulldog clamp 6 cm long and an arterial bulldog clamp 3 cm long respectively (Ativanichayaphong et al., 2008). Each stimulus was applied for 10 s and with an inter-stimulus interval of 20s.