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Research Report

Differential roles of ERK, JNK and p38 MAPK in pain-related spatial and temporal enhancement of synaptic responses in the hippocampal formation of rats: Multi-electrode array recordings

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ABSTRACT

It is known that chronic pain affects various higher brain functions including perception, emotion, cognition, and memory. However, few studies have been performed to examine pain-induced synaptic plastic changes in the hippocampal formation (HF), an important region subserving affective-motivational component of pain. Our previous study has revealed a strong impact of peripheral persistent nociception on synaptic connection, transmission and function in the HF of rats, in both temporal and spatial domains, by using a newly developed MED64 multichannel recording system. However, the underlying signaling mechanisms for this pain-related spatial and temporal plasticity are still less understood. As an initial investigation, the present study attempted to examine potential different roles of the mitogen-activated protein kinase (MAPK) members in mediating this plastic phenomenon. By virtue of the three well-known MAPK inhibitors targeting extracellular signal-regulated kinase (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK), respectively, in combination with the well-established MED64 multisite recording system, we found that pharmacological inhibition of the ERK- and JNK-mediated signaling pathway, at the plateau phase of the long-term potentiation (LTP), significantly decreased pain-enhanced LTP maintenance whereas similar blockade of p38 MAPK pathway dramatically further increased the potentiation. Regarding the spatial magnification of pain, ERK and p38 MAPK seemed to play opposing roles, with the former positively involved and the latter negatively involved, without any detectable effect of the JNK signaling pathway. Together, these results suggest differential roles of the specific members of the MAPK family in mediating pain-associated spatial and temporal plasticity in the HF, which are in good

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agreement with previous observations. In addition, a possible mechanistic separation between spatial and temporal magnification of pain is also indicated in this study.
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1. Introduction

Cumulating efforts from many laboratories over the past years have allowed the more clear dissection of the roles of hippocampal formation (HF) in pain processing (Liu and Chen, 2009). Indeed, there have been substantial anatomical (Amaral and Witter, 1989; van Strien et al., 2009), behavioral (Mckenna and Melzack, 2001; Soleimannejad et al., 2006; Favaroni Mendes and Menescal-de-Oliveira, 2008), electrophysiological (Sinclair and Lo, 1986; Khanna, 1997; Zheng and Khanna, 2008), molecular/biochemical (Aloisi et al., 1997; Duric and McCarson, 2007; Guo et al., 2007) and functional imaging (Derbyshire et al., 1997; Peyron et al., 1999; Ploghaus et al., 2001; Apkarian et al., 2005; Shih et al., 2008) evidence supporting the putative relationship between the HF and affective/motivational component of pain perception. Given the mechanistic similarity between pain and memory (Ji et al., 2003; Sandkühler, 2007), our previous study examined the potential effects of peripheral persistent nociception on spatial and temporal plasticity of synaptic connection and function in the HF, using a unique planar multi-electrode array (pMEA) technique, namely the newly developed 64-channel multi-electrode dish (MED64) system, in combination with the two-dimensional current source density imaging on acute hippocampal slices (Zhao et al., 2009). The results revealed a strong impact of peripheral persistent nociception on synaptic connection, transmission and function in the rat HF, in both temporal and spatial domains (Zhao et al., 2009). Nonetheless, the underlying signaling mechanisms for this pain-related spatial and temporal plasticity remain less clear.

There have been growing pieces of compelling evidence supporting the functional involvement/importance of the mitogen-activated protein kinase (MAPK) family of signal transduction molecules (Widmann et al., 1999), including extracellular signal-regulated kinase (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK), in the pathophysiological processes of inflammatory or neuropathic pain (Ji, 2004; Ji and Strichartz, 2004; Obata and Noguchi, 2004; Ji et al., 2009). Phosphorylated forms of ERK, p38 MAPK or JNK have been shown to act in either peripheral nociceptors or second-order dorsal horn neurons to produce exaggerated pain sensation by both post-translational modification of existing proteins and transcriptional modulation of expression of key genes (Wang et al., 2004; Mizushima et al., 2005; Cao et al., 2007; Xu et al., 2007; Zhuang et al., 2007; Hao et al., 2008; Wen et al., 2009; Gao et al., 2009, 2010). In addition, recent studies have also indicated that MAPKs may play central roles in the development of synaptic plasticity and learning/memory (Kornhauser and Greenberg, 1997; Impey et al., 1999; Sweatt, 2004; Thomas and Huganir, 2004). First, the ERK signaling pathway has been shown to be required for both NMDA-dependent (English and Sweatt, 1997; Impey et al., 1998; Winder et al., 1999; Morozov et al., 2003) and NMDA-independent (Coogan et al., 1999a; Kanterewicz et al., 2000) long-term potentiation (LTP) in both CA1 and dentate gyrus (DG) regions of the HF. Second, several pieces of evidence have been accumulated suggesting critical roles of ERK-mediated pathway in various forms of memory consolidation (Atkins et al., 1998; Berman et al., 1998; Blum et al., 1999; Schafe et al., 1999; Morozov et al., 2003). Third, both p38 MAPK and JNK pathway have also been demonstrated to be tightly associated with depotentiation or long-term depression (LTD) of hippocampal synapses (Coogan et al., 1999b; Bolshakov et al., 2000; Curran et al., 2003; Zhu et al., 2002, 2005). Albeit with these excitements, so far, little is known about the specialized, particular role of each member of the MAPKs in mediating pain-evoked synaptic plasticity in the HF.

In the present study, we performed pMEA recordings on acute hippocampal slices obtained from persistent pain-experiencing rats and investigated potential different roles of MAPK members in nociception-induced spatial and temporal plasticity in the HF. Specifically, three kinds of MAPK inhibitors, blocking activation of ERK by U0126 (Favata et al., 1998), p38 MAPK by SB239063 (Underwood et al., 2000) and JNK by SP600125 (Bennett et al., 2001), respectively, were separately bath applied during electrophysiological recording with the MED64 multichannel system to observe possible drug-evoked alterations in functional connectivity and plasticity of synaptic responses in hippocampal slices. The animal pain model we used is the bee venom (BV) test, a well-developed animal model of inflammatory pain mimicking honeybee sting-evoked natural tissue injury (Lariviere and Melzack, 1996; Chen et al., 1999; Chen and Lariviere, 2010). Our working hypothesis is that different members of the MAPK signaling family might play disparate even opposite roles in pain-related synaptic plasticity in the HF. Moreover, spatial and temporal magnification of pain may bear different signaling mechanisms for their full expression.

2. Results

2.1. *Differential roles of MAPK family members in pain-enhanced hippocampal LTP*

Given the huge numbers of previous papers reporting important roles of the MAPK family of signaling molecules in pathological pain as well as in synaptic plasticity (Ji, 2004; Sweatt, 2004; Thomas and Huganir, 2004; Ji et al., 2009), we first explored the effects of three MAPK inhibitors on pain-related temporal plasticity, namely the maintenance phase of LTP enhancement in HF (Zhao et al., 2009). All three drugs were separately bath applied to different slices at 2 h after LTP induction (the plateau phase of hippocampal LTP expression). Figs. 1–3 showed typical examples of multisite electrophysiological recordings, presenting changes in the magnitude of LTP caused by bath application of U0126 (40 μM), SP600125 (40 μM) and SB239063 (40 μM), respectively, on the BV-treated group of slices. The results demonstrated that pharmacological inhibition of ERK and JNK activation significantly reduced pain-enhanced LTP in both DG and CA1 area (Figs. 1 and 2), while

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