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MAPK activation in nociceptive neurons and pain hypersensitivity

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Abstract

Extracellular signal-regulated protein kinase (ERK) is a mitogen-activated protein kinase (MAPK) that mediates intracellular signal transduction in response to a variety of stimuli. ERK is involved in cell proliferation and differentiation and in neuronal plasticity, including long-term potentiation, learning, and memory. Here, we present recently accumulating data about the roles of MAPK pathways in mediating the neuronal plasticity that contributes to pain hypersensitivity. The phosphorylation of ERK in the dorsal root ganglion (DRG) and dorsal horn neurons occurs in response to noxious stimulation of the peripheral tissue or electrical stimulation to the peripheral nerve, i.e., activity-dependent activation of ERK in nociceptive neurons. In addition, the activation of ERK occurs in these nociceptive neurons after peripheral inflammation and axotomy and contributes to persistent inflammatory and neuropathic pain, via transcriptional regulation of key gene products. On the other hand, peripheral inflammation and axotomy also induces p38 MAPK activation in DRG neurons. Taken together, these findings indicate that activation of MAPK in nociceptive neurons may participate in generating pain hypersensitivity through transcription-dependent and -independent means. Thus, inhibition of MAPK signaling in the primary afferents, as well as in the spinal cord, may provide a fruitful strategy for the development of novel analgesics.

Keywords: Extracellular signal-regulated protein kinase; p38 mitogen-activated protein kinase; BDNF; Dorsal root ganglion; Spinal cord; Nociceptive neurons; Microglia; Pain stimuli; Inflammatory pain; Neuropathic pain

Introduction

The mitogen-activated protein kinase (MAPK) is a family of serine/threonine protein kinases that transduce extracellular stimuli into intracellular posttranslational and transcriptional responses (Seger and Krebs, 1995; Lewis et al., 1998; Widmann et al., 1999). The MAPK family includes extracellular

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signal-regulated protein kinase (ERK), p38 MAPK, c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and ERK5. The ERK is activated by membrane depolarization and calcium influx (Rosen et al., 1994), activated by an upstream kinase, MAPK/ERK kinase (MEK), and known to be one of the intracellular signaling pathways involved in neuronal plasticity, such as long-term potentiation, learning, and memory (Fields et al., 1997; Martin et al., 1997; Fields, 1998; Impey et al., 1999; Sweatt, 2001). Physiological and pathological activity-dependent activation of ERK occurs in the CNS, especially in the hippocampus (Baraban et al., 1993; English and Sweatt, 1996; Atkins et al., 1998; Obrietan et al., 1998; Dudek and Fields, 2001). Recently, several studies have reported ERK phosphorylation in the nociceptive pathway; for example, acute noxious stimuli, such as formalin or capsaicin, induce ERK phosphorylation in spinal dorsal horn neurons (Ji et al., 1999; Huang et al., 2000; Karim et al., 2001; Pezet et al., 2002a,b). A MEK inhibitor PD 98059 reduces acute pain behavior after subcutaneous formalin injection, suggesting a role for ERK in acute nociceptive processing by a nontranscriptional mechanism, given the short time involved (30–60 min) (Ji et al., 1999; Karim et al., 2001). Neuronal plasticity occurs in primary afferent neurons, as well as spinal dorsal horn neurons (Woolf and Costigan, 1999; Woolf and Salter, 2000; Julius and Basbaum, 2001; Scholz and Woolf, 2002). This review will mainly focus on the dorsal root ganglion (DRG) neurons and will review the contribution of the MAPK pathways in nociceptive neurons to pain hypersensitivity.

ERK activation in DRG neurons after noxious stimulation

Much attention has focused on the signal transduction mechanisms of primary afferent neurons responsible for the modulation of pain transmission. Inflammatory mediators, such as prostaglandin E_2, serotonin, epinephrine, and nerve growth factor (NGF), produce hyperalgesia through activation of protein kinase A (PKA) or protein kinase C (PKC) in primary afferent neurons (Gold et al., 1998; Khasar et al., 1999). Recently, it has been shown that the ERK cascade acts in epinephrine-induced hyperalgesia; also, the Ras-MEK-ERK pathway is activated independently of PKA or PKC (Aley et al., 2001; Dina et al., 2003). Furthermore, NGF injected into the peripheral tissue increases p-ERK labeling in tyrosine kinase A (trkA)-containing DRG neurons (Averill et al., 2001; Delcroix et al., 2003). However, there have been few studies of signal transduction involved in the activity-dependent plasticity of primary afferent neurons (Fields et al., 1997; Fitzgerald, 2000). We have demonstrated recently that phosphorylation of ERK in primary afferent neurons occurs in response to noxious stimulation of the peripheral tissue or electrical stimulation to the peripheral nerve, i.e., activity-dependent activation of ERK in DRG neurons (Dai et al., 2002). In addition, a MEK inhibitor U0126 dose-dependently attenuates thermal hyperalgesia after capsaicin injection. These results suggest that the activation of ERK pathways in DRG neurons is involved in peripheral sensitization in acute pain conditions. The phosphorylation of ERK in DRG neurons after noxious stimulation might be useful for examining the activation state of each neuron that contains various pain-related molecules (Dai et al., 2002).

ERK activation and gene expression in spinal neurons

Recently, several studies have reported that ERK may have a role in persistent hyperalgesia (hypersensitivity to thermal and mechanical stimuli), a feature of chronic pain states (Sammons et

al., 2000; Ji et al., 2002a; Galan et al., 2002). Persistent inflammatory hyperalgesia can be induced by paw inflammation with carrageenan or complete Freund's adjuvant (CFA). Spinal ERK is phosphorylated by these stimuli (Ji et al., 2002a; Galan et al., 2002), and inflammatory hyperalgesia can be prevented by ERK inhibitors (Sammons et al., 2000; Ji et al., 2002a). Furthermore, spinal ERK is also activated in experimental neuropathic and visceral pain models (Ciruela et al., 2003; Galan et al., 2003). The ERK produces not only short-term functional changes by nontranscriptional processing, but also long-term adaptive changes by increasing gene transcription. For example, activated ERK translocates from the cytoplasm to the nucleus and activates Rsk2, which then phosphorylates the transcription factor cAMP response element-binding protein (CREB) on Serine 133 (Xing et al., 1996). The phosphorylated CREB then binds to the cAMP response element sites on the promoter regions of the DNA and initiates the transcription of genes (English and Sweatt, 1997; Atkins et al., 1998; Impey et al., 1998, 1999; Obrietan et al., 1999). In fact, peripheral inflammation and nerve injury induce CREB phosphorylation in dorsal horn neurons (Ji and Rupp, 1997; Messersmith et al., 1998; Ma and Quirion, 2001; Miletic et al., 2002; Hoeger-Bement and Sluka, 2003). However, apart from immediate early genes such as c-fos, the specific target genes regulated by ERK are primarily unknown (Xing et al., 1996; Sgambato et al., 1998). Ji and colleagues recently demonstrated that the activation of the ERK in dorsal horn neurons contributes to persistent inflammatory pain, via transcriptional regulation of prodynorphin and neurokinin-1 (Ji et al., 2002a).

ERK activation and gene expression in DRG neurons

The ERK pathway involvement in neurotrophin-dependent survival and differentiation of developing peripheral neurons has been characterized in detail (Klesse and Parada, 1999; Miller and Kaplan, 2001; Patapoutian and Reichardt, 2001). For example, the high-affinity receptor for NGF, trkA, can signal through at least six different pathways, a major one of which is a MAPK pathway (i.e., the ERK pathway; Finkbeiner, 2000; Chang and Karin, 2001). In this pathway, activated receptors induce GTP loading and activation of the small G-protein Ras. In turn, Ras-GTP recruits a three-tiered enzyme cascade in which a MAPK kinase kinase (Raf) phosphorylates MEK, which phosphorylates and activates ERK (English et al., 1999). However, very little is known about the ERK pathway, responsible for the maintenance of the nociceptive phenotype of adult sensory neurons and the changes after peripheral inflammation and nerve injury. Furthermore, it is not clear what role these changes play in generating pain hypersensitivity (Woolf and Costigan, 1999; Ji and Woolf, 2001). Inflammation and nerve injury lead to altered gene transcription and protein synthesis in DRG neurons (Hokfelt et al., 1994; Noguchi et al., 1995; Fukuoka et al., 1998; Alvares and Fitzgerald, 1999; Woolf and Salter, 2000; Fukuoka and Noguchi, 2002). For example, brain-derived neurotrophic factor (BDNF) synthesis is known to increase in trkA-expressing small and medium-sized DRG neurons after inflammation (Apfel et al., 1996; Michael et al., 1997; Kerr et al., 1999; Mannion et al., 1999; Thompson et al., 1999; Obata et al., 2002), whereas after nerve injury, the increase in BDNF occurs in the axotomized medium-to-large diameter DRG neurons (Cho et al., 1998; Tonra et al., 1998; Li et al., 1999; Michael et al., 1999; Zhou et al., 1999b; Obata et al., 2003a).

Recently, we have shown that the activation of ERK regulates gene expression of BDNF in primary afferent neurons after peripheral inflammation and sciatic nerve transection (Obata et al.,

2003b). Peripheral inflammation induces an increase in the phosphorylation of ERK, mainly in trkA-containing small-to-medium diameter DRG neurons 1 d after the CFA injection (Fig. 1A, B). The treatment of the MEK inhibitor U0126 reverses the pain hypersensitivity and the increase in phosphorylated-ERK (p-ERK) and BDNF in DRG neurons induced by CFA. In contrast, axotomy induces the activation of ERK mainly in medium- and large-sized DRG neurons and in satellite glial cells at 3, 7, and 14 d after the nerve lesion (Fig. 1C, D). U0126 suppresses the axotomy-induced autotomy behavior and reverses the increase in p-ERK and BDNF. To elucidate whether alterations of endogenous NGF can trigger changes in both the phosphorylation of ERK and BDNF expression similar to those seen after peripheral inflammation and axotomy, intrathecal injections of rat recombinant β-NGF or anti-NGF were performed. In this test, the intrathecal application of NGF induced an increase in the number of p-ERK- and BDNF-labeled cells, mainly small neurons, and the application of anti-NGF induces an increase in p-ERK and BDNF in some medium-to-large diameter DRG neurons. These findings suggest that the activation of ERK in the primary afferents occurs in different populations of DRG neurons after peripheral inflammation and axotomy, respectively, through alterations in the target-derived NGF and contributes to persistent inflammatory

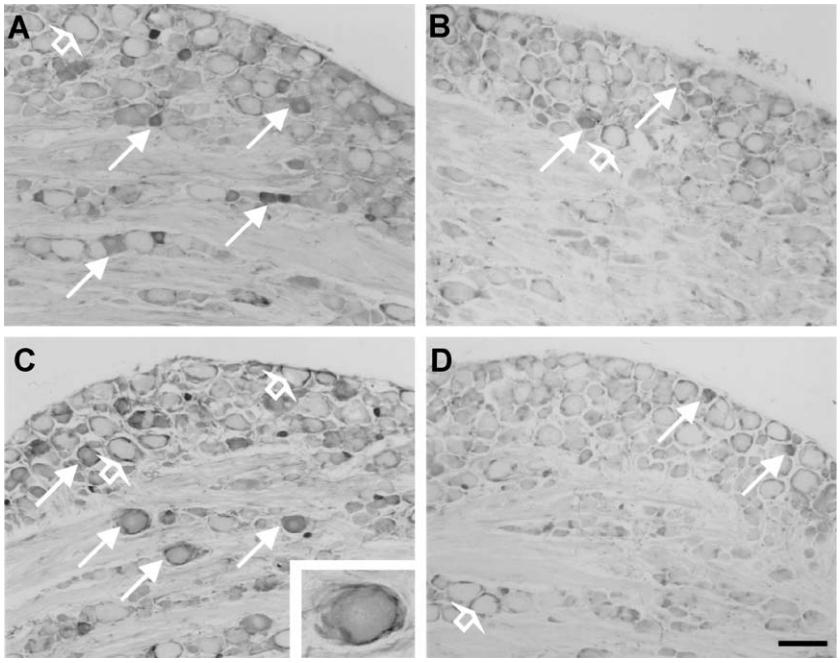

Fig. 1. A, B, Photomicrographs showing the p-ERK-IR in the ipsilateral (A) and contralateral (B) L4/5 DRG 1 d after peripheral inflammation. There was an increase in the number of p-ERK-IR neurons in the ipsilateral DRG (arrows). In contrast to DRG neurons, satellite cells show high basal levels of p-ERK-IR (open arrows). C, D, Photomicrographs showing the p-ERK-IR in the ipsilateral (C) and contralateral (D) L4/5 DRG 7 d after sciatic nerve transection. Axotomy increased p-ERK expression in neurons and/or satellite cells in the ipsilateral DRG. The p-ERK-IR was present in both neurons and surrounding satellite cells (arrows) or only in satellite cells (open arrows); the inset shows that both the neuron and surrounding satellite cell expressed p-ERK-IR. Scale bar: (in D) A–D, 100 μm.

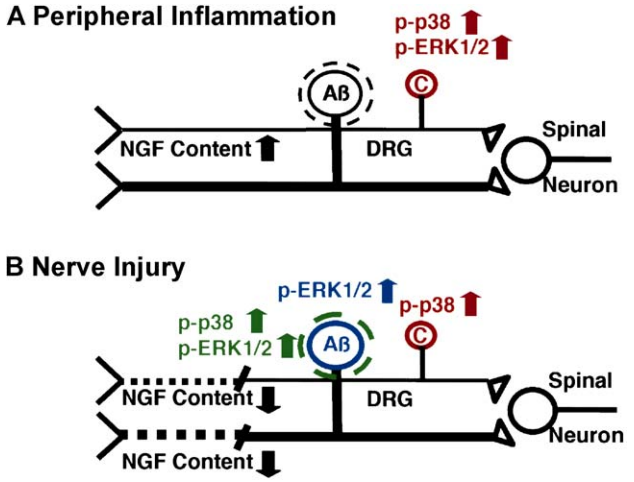

Fig. 2. Schematic representation of the expression of ERK and p38 after peripheral inflammation and axotomy. A, After peripheral inflammation, ERK, as well as p38, is activated in small sized neurons, secondary to the increase of target-derived NGF. B, After nerve injury, ERK is activated in large-sized neurons, whereas p38 is activated in small sized neurons, secondary to the loss of target-derived NGF. Furthermore, the increase in both p-ERK- and p-p38-IR was seen in satellite glial cells, surrounding large-sized neurons.

and neuropathic pain, via transcriptional regulation of BDNF expression (Fig. 2) (Obata et al., 2003b).

p38 activation and gene expression in DRG neurons

A recent report demonstrated that transient receptor potential ion channel TRPV1, formerly known as vanilloid receptor-1, is regulated by NGF-induced activation of the ERK/MAPK pathway in DRG neurons in vitro (Bron et al., 2003). On the other hand, Ji and colleagues showed that p38 MAPK activation in the DRG is required for NGF-induced increases in TRPV1 expression and contributes to the maintenance of inflammatory pain hypersensitivity (Ji et al., 2002b). p38, a MAPK which operates through a separate intracellular cascade, functions as a mediator of cellular stresses such as inflammation and apoptosis (Widmann et al., 1999; Shi and Gaestel, 2002). Although an activity-dependent p38 activation occurs in neurons (Mao et al., 1999), and p38 exerts effects in the hippocampus that oppose that of ERK (Bolshakov et al., 2000), the contribution of p38 MAPK to nociception and pain hypersensitivity is still under investigation. Recent reports have demonstrated that not only peripheral inflammation but also axotomy induces p38 activation in small DRG neurons (Fig. 2) (Ji et al., 2002b; Kim et al., 2002; Jin et al., 2003; Schafers et al., 2003). A p38 inhibitor SB203580 reduces inflammation-induced thermal hyperalgesia and L5 spinal nerve ligation-induced mechanical allodynia (Ji et al., 2002b; Jin et al., 2003; Schafers et al., 2003). Considering that ERK activation occurs in different populations of DRG neurons after peripheral inflammation and axotomy, ERK and p38 are likely to have distinct roles in pain states evoked by several different mediators and pathological conditions (Fig. 2).

In addition to ERK and p38, other MAPK pathways, such as the JNK/SAPK or ERK5 pathway, also may be activated by inflammation and/or nerve injury (Kenney and Kocsis, 1998; Ma et al., 2001; Watson et al., 2001). Peripheral axotomy has been shown to induce long-term JNK/SAPK activation in DRG neurons. Long-lasting JNK/SAPK activation and c-Jun expression may participate in gene regulation (Kenney and Kocsis, 1998; Fernyhough et al., 1999; Hou et al., 2003). Furthermore, phosphorylation of JNK/SAPK, as well as ERK and p38, plays a role in the morphine-induced increase in calcitonin gene-related peptide and substance P in primary sensory afferents, contributing to the development of tolerance to opioid-induced analgesia (Ma et al., 2001). Watson and colleagues reported that not only ERK but also ERK5 mediates nuclear responses following direct cell body stimulation by NGF, whereas during retrograde signaling, endocytosed trks activate the ERK5 (Watson et al., 2001). These findings suggest that JNK/SAPK and ERK5, as well as ERK and p38, play an important role in the generation of pain hypersensitivity.

MAPK activation in non-neuronal cells

The activation of spinal cord glial cells, including microglia and astrocytes, has been implicated in the pathogenesis of pain (Meller et al., 1994; Watkins et al., 1997, 2001a,b; DeLeo and Yezierski, 2001; Tsuda et al., 2003). Proinflammatory cytokines released from glial cells produce pain hypersensitivity, and microglia and astrocytes are activated in the spinal cord after peripheral inflammation and nerve injury and in cancer models (Fu et al., 1999; Sweitzer et al., 1999; Winkelstein et al., 2001; Mantyh et al., 2002). p-p38 is present constitutively in non-neuronal cells in the spinal cord, and peripheral inflammation induces only a modest increase in p-p38 levels (Ji et al., 2002b). In contrast, peripheral axotomy induces p38 activation in spinal microglia (Nomura et al., 2001; Kim et al., 2002; Jin et al., 2003). p38 inhibitors diminish inflammation-induced hyperalgesia and pain hypersensitivity in the sciatic inflammatory neuropathy model by blockade of spinal p38 activation (Watkins et al., 1997; Milligan et al., 2000, 2003; Svensson et al., 2003a,b). On the other hand, ERK and JNK/SAPK, but not p38, are phosphorylated in astrocytes in the spinal cord after partial nerve injury (Ma and Quirion, 2002), whereas dorsal rhizotomy induces ERK activation in spinal microglia and oligodendrocytes (Cheng et al., 2003).

In the DRG, p-ERK expression was upregulated in satellite glial cells that surrounded, in particular, the larger diameter neuronal somata after sciatic nerve transection (Fig. 2) (Obata et al., 2003b). In addition, peripheral axotomy induces p38 activation in satellite cells surrounding neurons in the DRG (Fig. 2) (Jin et al., 2003). These findings emphasize the importance of glial cells and glial-neuronal interactions in the DRG, as well as in the spinal cord, after peripheral axotomy (McLachlan and Hu, 1998; Ramer et al., 1999; Zhou et al., 1999a; Hu and McLachlan, 2002).

Conclusion

Activation of MAPK clearly has a substantial role in the establishment and maintenance of nociceptive-induced plasticity in DRG and dorsal horn neurons not only by posttranslational modifications of target proteins, but also by increasing gene transcription. These attractive targets of study will give us new approaches for understanding the cellular/molecular mechanisms underlying pain hyper-

sensitivity. In addition, MAPK pathways have several components, affording an opportunity for antagonism at many levels. Therefore, MAPK pathways in the primary afferents, as well as in the spinal cord, may be potential targets for pharmacological intervention.

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