Progress in Neuro-Psychopharmacology & Biological Psychiatry 60 (2015) 77–92

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

ERK1/2: Function, signaling and implication in pain and pain-related anxio-depressive disorders

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ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form 31 January 2015
Accepted 15 February 2015
Available online 21 February 2015

Keywords:
Anxiety
Chronic pain
Depression
Paragigantocellularis–locus coeruleus–prefrontal cortex pathway
pERK1/2

ABSTRACT

Despite the increasing knowledge regarding pain modulation, the understanding of the mechanisms behind a complex and pathologic chronic pain condition is still insufficient. These knowledge gaps might result in ineffective therapeutic approaches to relieve painful sensations. As a result, severe untreated chronic pain frequently triggers the onset of new disorders such as depression and/or anxiety, and therefore, both the diagnosis and treatment of patients suffering from chronic pain become seriously compromised, prompting a self-perpetuating cycle of symptomatology. The extracellular signal-regulated kinases 1 and 2 (ERK1/2) are molecules strongly implicated in the somatic component of pain at the spinal cord level and have been emerging as mediators of the emotional-affective component as well. Although these molecules might represent good biomarkers, their use as pharmacological targets is still open to discussion as paradoxical information has been obtained. Here we review the current scientific literature regarding ERK1/2 signaling in the modulation of pain, depression and anxiety, including the emotional-affective spheres of the pain experience.

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Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; ACC, anterior cingulate cortex; AMY, amygdala; BBB, blood–brain barrier; BD, bladder distension; BDNF, brain-derived neurotrophic factor; CCAN, capsular central amygdaloid nucleus; CCI, chronic constriction injury; CD, colorectal distension; CFA, complete Freund's adjuvant; CIC, cyclophosphamide-induced cystitis; CMS, chronic mild stress; CRF2, corticotrophin-releasing factor receptor 2; DRG, dorsal root ganglia; DRN, dorsal raphe nucleus; ERK1/2, extracellular signal-regulated kinases 1 and 2; EW, Edinger-Westphal nucleus; FSS, forced swimming stress; GiA, nucleus reticularis gigantocellularis pars alpha; InC, inferior colliculus; IS, immobilization stress; LC, locus coeruleus; LPB, lateral parabrachial nucleus; LRt, lateral reticular nucleus; MAPK, mitogen-activated protein kinase; MIA, OA – monosodium iodoacetate-induced osteoarthritis; NA, noradrenaline; OIA, ovariectomy-induced abdominal hyperalgesia; PAG, periaqueductal gray matter; pERK1/2, phosphorylated ERK1/2; PFC, prefrontal cortex; PGi, paragigantocellularis nucleus; PrH, prepositus hypoglossi; PVN, paraventricular nucleus; RMg, nucleus raphe magnus; RS, restraint stress; RVM, rostral ventromedial medulla; SC, spinal cord; SCI, spinal cord injury; ScNI, sciatic nerve injury; SNI, spinal nerve injury; SNL, spinal nerve ligation; SP, substance P; STZ, streptozotocin; SuC, superior colliculus; tERK1/2, total ERK1/2; TN, trigeminal neuropathy; TSN, trigeminal spinal nucleus; VTA, ventral tegmental area.

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http://dx.doi.org/10.1016/j.pnpbp.2015.02.010
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1. Introduction

The ability to feel pain when something threatens the organism is a common defense strategy of the body. Thus, feeling pain, in normal conditions, is beneficial. However, for reasons not completely understood, this alarm may become permanently activated leading to a persistent and/or prolonged painful state, without any apparent physiological/biological value. Consequently, it causes a great disability in patients when performing normal daily tasks. In Europe, chronic pain affects a great number of individuals (Azevedo et al., 2012; Breivik et al., 2006), with the inconvenience that their families and the surrounding social environment are also affected, representing substantial costs to health-related governmental services (Reid et al., 2011). Unfortunately, chronic pain treatment is often refractory to many pharmacological approaches, and therefore, the search for new effective drug targets to attenuate pain is urgent. Additionally, when patients go through a wide range of inefficient treatments, some other unpleasant symptoms associated to the chronic pain condition may emerge, such as depression, anxiety and self-perceived stress (Aguera et al., 2010; Aguera-Ortiz et al., 2011; Blackburn-Munro and Blackburn-Munro, 2001; Breivik et al., 2006; Díaz Cabezas et al., 2009), aggravating the clinical diagnosis of the patient (Jain et al., 2011) as well as its treatment. Indeed, the emotional aspect is also implicated in pain sensation, as recognized in the definition proposed by the International Association for the Study of Pain, which states that pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Such relation is clear when some patients that are diagnosed with depression, also display altered pain perception and low tolerance and thresholds to painful stimulation (Kundermann et al., 2009). Moreover, the diagnosis of depression and pain disorders in the same patient is common (Bair et al., 2003). So far, it is recognized that both conditions share common neurobiological pathways and neurotransmitters (Delgado, 2004; Robinson et al., 2009), but it is unclear how they are modulated when co-prevalence of chronic pain and depression occurs. Interestingly, antidepressants have been prescribed for attenuation of pain associated with neuropathy (Davis, 2010; Finnerup et al., 2010; Mico et al., 2006; Woolf and Mannion, 1999). Thus, it is well-defined that chronic pain involves much more than a simple mechanism and that all its complexity must be taken in consideration for effective treatment. Moreover, it is not completely understood whether a causal relationship between pain and depression/anxiety exists or rather if there is a higher individual predisposition for developing one condition when the other is diagnosed. These are important reasons for studying new approaches, common pharmacological targets and neuroanatomical pathways. In this regard, the expression of activated extracellular signal-regulated kinases 1 and 2 (ERK1/2) has emerged as a valuable and promising molecular biomarker and target, particularly in encephalic structures implicated both in pain and pain-associated mood disorders, such as the noradrenergic–locus coeruleus system (NA–LC; Alba-Delgado et al., 2013; Borges et al., 2014).

2. The ERK1/2 cascade

In the last years, the study of intracellular signaling targets as a measure of the cellular processes occurring following specific experimental conditions has been intense. In the pain field, one of the most well-known is the mitogen-activated protein kinase (MAPK) superfamily, which is evolutionarily conserved across species (Ji et al., 2009). Within this superfamily, ERK1 and ERK2 were the first kinases to be identified. They have a high similarity, sharing many physiological/biological functions and being commonly referred together as ERK1/2. These two kinases are activated together by phosphorylation produced by upstream MEK1 and MEK2 (MAP/ERK kinases 1 and 2) in the Ras–Raf–MEK–ERK cascade, as shown in Fig. 1A (Ji et al., 2009). ERK1/2 are ubiquitously expressed either in the activated (phosphorylated-pERK1/2) and/or inactivated states. Once activated, pERK1/2 can be translocated into the nucleus in order to activate, for instance, a wide range of transcriptional factors, or simply remain in the cytoplasm, regulating other sub-cellular functions (Fig. 1A). The development of specific antibodies for the detection of phosphorylated isoforms of ERK1/2 represented a huge step for increasing our knowledge regarding the implication of these kinases in a wide range of experimental conditions. The most common way of quantifying pERK1/2 expression is by immunohistochemistry, either by counting positive immunoreactive-cells or by densitometry, or by western blot, through measuring the signal given by the pERK1/2 bands relatively to that of total ERK1/2 (tERK1/2, which consists of the total level of ERK1/2 protein independently of the phosphorylation state). In general, the immunodetection of pERK1/2 in basal conditions is rare, being practically absent at the spinal cord while low levels are detected at the supraspinal level. However, strongly painful stimuli of short duration are able to trigger ERK1/2 activation, at least at the spinal cord level (Bobrovskaya et al., 2001; Ji et al., 1999). The immunoreactivity for pERK1/2 can be observed in multiple organelles and cellular structures, as is the soma, nucleus, axons and dendrites, having the advantage of allowing the study of cell morphology (Fig. 1B; Flood et al., 1998; Koh et al., 2002). In healthy conditions, after exerting its physiological function, the normal tracking of the ERK1/2 signaling cascade is dephosphorylation. Several pathological conditions, including pain syndromes, cancer and depressive disorders, might deregulate the normal course of the Ras–Raf–MEK–ERK cascade, causing a persistent activation or even inactivation of ERK1/2, and, therefore this cascade is an interesting target for basic and translational research, including for drug development for therapeutic purposes (Einat et al., 2003; Ma and Quirion, 2005; Roberts and Der, 2007).

3. ERK1/2 activation as an important signaling pathway in pain

Several pain conditions were shown to induce phosphorylation of ERK1/2 (Ji et al., 2009) at different levels of the pain processing pathways, such as the dorsal root ganglia (DRG), spinal cord and some supraspinal structures (see Table 1). Such phosphorylation is a sign of activation of intracellular mechanisms, indicating that noxious stimulation triggered this signaling cascade. Moreover, many pain-related studies have investigated the effects of ERK1/2 inhibitors (see Table 2), whose main mechanism of action is to prevent the phosphorylation of the ERK 1 and 2 by the upstream kinases, MEK 1 and 2 (Fig. 1A). The main results obtained so far strongly suggest that ERK1/2 may represent a valid therapeutic target in pain conditions (Ciruela et al., 2003; Ji et al., 2007; Zhang et al., 2005). Additionally, ERK1/2 has been associated with the affective/emotional component of pain (see Table 3). Finally, it has also been proposed that ERK1/2 might be

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