Progress in Neurobiology 116 (2014) 13–32

Contents lists available at ScienceDirect

Progress in Neurobiology

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

Preclinical research on pain comorbidity with affective disorders and cognitive deficits: Challenges and perspectives

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ARTICLE INFO

Article history:
Received 13 June 2013
Received in revised form 31 December 2013
Accepted 2 January 2014
Available online 18 January 2014

Keywords:
Chronic pain
Comorbidity
Emotional disorder
Cognitive impairment
Synaptic plasticity
Animals

ABSTRACT

Affective disorders and cognitive deficits are common comorbidities of chronic pain in the clinical setting, which severely affect the quality of life of pain patients and impose a great difficulty upon clinical pain therapy. Despite large numbers of human studies examining this issue, there are surprisingly few reports investigating the comorbidities of chronic pain in animal models. This review summarizes and integrates previous reports of animal studies on pain and comorbidity, covering pain-evoked anxiety, depression, attentional deficits, cognitive impairment and locomotor dysfunction in rodents. Moreover, pain-induced alterations in synaptic plasticity are also discussed in terms of long-term potentiation and long-term depression, synaptic transmission, neuronal excitability and structural correlates in 'pain matrix'. Finally, we conclude this review by pointing out some unresolved problems and future research directions.

Contents

Abbreviations: ACC, anterior cingulate cortex; ALB, anxiety-like behavior; BDNF, brain-derived neurotrophic factor; BLA, basolateral nuclei of amygdala; BrDU, bromodeoxyuridine; BV, bee venom; CCI, chronic constriction injury; CeA, central nuclei of amygdala; CeLC, laterocapsular part of the central nucleus; CFA, complete Freund's adjuvant; CNS, central nervous system; CPN, common peroneal nerve; CRF, corticotropin-releasing factor; DG, dentate gyrus; DLB, depression-like behavior; EPM, elevated plus maze; EPSPs, excitatory postsynaptic potentials; ERK, extracellular signal-regulated kinase; FST, forced swim test; HIV-1, human immunodeficiency virus type I; IC, insular cortex; LTD, long-term depression; LTP, long-term potentiation; MRI, magnetic resonance imaging; MWM, Morris water maze; OF, open field; PFC, prefrontal cortex; PKC, protein kinase C; PSNL, partial sciatic nerve ligation; PTP, post-tetanic potentiation; S1, primary somatosensory cortex; SNI, spared nerve injury; SNL, spinal nerve ligation; SNT, spinal nerve transection; STZ, streptozotocin; TNFα, tumor necrosis factor α; UCMS, unpredictable chronic mild stress; VZV, varicella zoster virus.

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http://dx.doi.org/10.1016/j.pneurobio.2014.01.003

1. Introduction

Pain is a complex experience consisting of sensory-discriminative, affective-motivational and cognitive-evaluative dimensions (Liu and Chen, 2009; Price, 2000). It is now widely accepted that noxious information is processed by a complicated and interconnected neural network ('neuromatrix') in the brain (Apkarian et al., 2009, 2011; Melzack, 2005). In the physiological state, acute pain has an adaptive and protective role: it serves as a warning system to alarm the body of imminent or actual tissue damage and assists wound repairing. Unlike physiological pain, however, chronic pathological pain is a major clinical problem, producing huge economic and social burdens (Latham and Davis, 1994; Smith and Torrance, 2012). When pain becomes persistent or severe, it becomes maladaptive and causes great suffering and distress. Both tissue inflammation and nerve system lesions can result in chronic pain, called inflammatory pain and neuropathic pain, respectively (Costigan et al., 2009; von Hehn et al., 2012; Woolf, 1999; Woolf and Mannion, 1999). Although the prevalence of chronic pain is quite high in human populations, the current treatment strategies against chronic pain are quite limited and most available analgesics used for pain treatment are associated with adverse side effects (Woodcock et al., 2007; Woolf, 2010).

One of the most important reasons for this unmet clinical need of chronic pain is the insufficient knowledge of the exact mechanisms underlying various types of chronic pain. In the past several decades, most basic research efforts have been focused on the peripheral and spinal mechanisms of pain (Basbaum et al., 2009; Chen et al., 2013a; Chen and Lariviere, 2010; Ji, 2004; Ji and Strichartz, 2004; Woolf and Salter, 2000). Actually, peripheral sensitization (Chen et al., 2013a; Chen and Lariviere, 2010; Gold and Gebhart, 2010; Hucho and Levine, 2007; Woolf and Ma, 2007) and central sensitization (Chen et al., 2013a; Chen and Lariviere, 2010; Kuner, 2010; Latremoliere and Woolf, 2009; Woolf, 2011) have been considered as major cellular mechanisms contributing to the sensory symptoms of chronic pain, such as spontaneous pain, hyperalgesia, and allodynia. Nevertheless, as mentioned above, pain is a three-dimensional experience that will be finally processed and modulated in the brain (Jaggi and Singh, 2011; Tracey and Mantyh, 2007). Unfortunately, much less attention has been directed at the cortical mechanisms of pain perception and modulation, which hampers the advances in pain therapy (Chen, 2009; Chen et al., 2013a; Neugebauer et al., 2009; Zhuo, 2007a, 2008, 2011). Therefore, it becomes more necessary and important to extend the pain research from lower levels of the 'pain matrix' into the higher level of cortical and subcortical brain structures (Chen, 2009; Chen et al., 2013a; Liu and Chen, 2009; Zhuo, 2008, 2011, 2012).

Another contributing factor to the intractable nature of chronic pain might be the existence of pain-related comorbidities such as anxiety, depression, amnesia, insomnia, and other forms of disabilities (Argoff, 2007; Asmundson and Katz, 2009; Bair et al., 2003; Giamberardno and Jensen, 2012). These comorbid symptoms could be caused by the persistence of pain experience *per se* or by the original etiologies of chronic pain, such as the diabetic neuropathy, traumatic nerve injury, post-herpetic neuralgia, central post-stroke pain and rheumatic arthritis. The comorbid emotional or cognitive disorders can negatively affect the life quality of the pain patients on one hand and further aggravate the sensory abnormalities of chronic pain on the other hand. Thus, it would be a challenging task to treat not only sensory symptoms of chronic pain but also to deal with the comorbidities accompanying the disease. A large number of previous studies have been performed to investigate the pain-associated comorbidities in human subjects and several reviews have been published in this regard (Campbell et al., 2003; Moriarty et al., 2011; Nicolson et al., 2009). Comparatively, however, less progress has been made in the preclinical work of comorbidities of chronic pain (Moriarty et al., 2011). Clinical research in this field is largely phenomenological, whereas animal models are the best source of the precise etiology and pathogenesis of pain and its comorbidities. Preclinical research in animals is thus a necessary and important step not only for increasing our understandings of the underlying mechanisms but also for promoting the development of therapeutic approaches to pain treatment. In this review, we present previous and recent evidence on pain-related comorbidities in animals, describing pain-evoked emotional disorders (anxiety and depression), cognitive dysfunctions (attentional deficits and memory impairment), locomotion changes, as well as alterations in synaptic plasticity in the central nervous system (CNS) that have been believed to underlie some of these comorbidities.

2. Pain and emotional disorders

Chronic pain is frequently accompanied by emotional disorders, such as anxiety and depression (Nicolson et al., 2009). These comorbid affective disorders can interfere with daily activities, thus exerting a major negative effect on the quality of life in chronic pain patients (Argoff, 2007; Asmundson and Katz, 2009; Campbell et al., 2003). In addition to large amounts of literature on pain and comorbidity in the human subjects, there have been increasing numbers of studies investigating this issue through animal models. Here, we will present some previous reports attempting to model the clinic phenomenon of pain-related affective disturbances and to examine the possible working mechanisms underlying this co-existence.

2.1. Pain and anxiety

Anxiety constitutes a frequently occurred mood disturbance in the clinic setting. The reciprocal relationship between anxiety and pain has been demonstrated by a large body of previous human research (Arntz et al., 1994; McWilliams et al., 2003; Ploghaus et al., 2001). Similarly, a variety of animal experiments have been conducted to assess pain-evoked anxiety-like behavior (ALB) in multiple types of preclinical models of pathological pain (Table 1). First, Schellinck and colleagues assessed the long-term behavioral