Progress in Neurobiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

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

Stress-induced hyperalgesia

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ARTICLE INFO

Article history:
Received 18 January 2014
Received in revised form 17 May 2014
Accepted 29 June 2014
Available online xxx

Keywords:
Pain
Stress
Human
Rodent
Anxiety
Brain

ABSTRACT

The importance of the modulation of pain by emotion is now widely recognised. In particular, stress and anxiety, depending on their nature, duration and intensity, can exert potent, but complex, modulatory influences typified by either a reduction or exacerbation of the pain state. Exposure to either acute or chronic stress can increase pain responding under experimental conditions and exacerbate clinical pain disorders. There is evidence that exposure to chronic or repeated stress can produce maladaptive neurobiological changes in pathways associated with pain processing, resulting in stress-induced hyperalgesia (SIH). Preclinical studies of SIH are essential for our understanding of the mechanisms underpinning stress-related pain syndromes and for the identification of neural pathways and substrates, and the development of novel therapeutic agents for their clinical management. In this review, we describe clinical and pre-clinical models used to study SIH and discuss the neural substrates, neurotransmitters and neuromodulatory systems involved in this phenomenon.

Contents

Abbreviations: 2-AG, 2-arachidonylglycerol; 5-HT, 5-hydroxytryptamine; ACC, anterior cingulate cortex; AEA, anandamide; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB_1, cannabinoid receptor 1; CB_2, cannabinoid type 2; CCK, cholecystokinin; CCK_2, cholecystokinin 2 receptor; CeA, central nucleus of the amygdala; CFA, complete Freund's adjuvant; CMS, chronic mild stress; CRF_1, corticotropin-releasing factor receptor subtype 1; CRF_2, corticotropin-releasing factor receptor subtype 2; DMH, dorsomedial hypothalamus; DRG, dorsal root ganglia; FAAH, fatty acid amide hydrolase; FSS, forced swim stress; GABA, gamma-aminobutyric acid; GFAP, glial fibrillary acidic protein; HPA, hypothalamo-pituitary-adrenal; IBS, irritable bowel syndrome; MD, maternal deprivation; MS, maternal separation; NA, noradrenaline; NMDA, N-methyl-D-aspartic acid; PAG, periaquaductal grey; PFC, prefrontal cortex; PND, post-natal day; PTSD, post-traumatic stress disorder; RVM, rostral ventromedial medulla; S1, somatosensory cortex; SART, specific alternation rhythm of temperature; SIH, stress-induced hyperalgesia; SNL, spinal nerve ligation; SSRI, selective serotonin receptor uptake inhibitor; TFL, tail flick latency; WAS, water avoidance stress; WKY, Wistar–Kyoto.

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http://dx.doi.org/10.1016/j.pneurobio.2014.06.003
0301-0082/

1. Introduction

The last couple of decades have witnessed an emerging and sustained interest among research scientists and clinicians in understanding the interactions between stress and pain. This interest has been driven by overwhelming clinical and preclinical evidence demonstrating complex and potent effects of stress on pain processing and responding. Critical scrutiny of these data suggests that the nature, duration and intensity of the stressor are key determinants of the effects of stress on pain. Numerous studies have demonstrated that exposure to an acute, robust, intense stress induces a reduction in pain responding, a phenomenon described as stress-induced analgesia (for review see Butler and Finn, 2009).

On the other hand, repeated or chronic exposure to physical or psychological stressors which may be anticipatory/anxiogenic in nature, typically results in the less well understood phenomenon of stress-induced hyperalgesia (SIH) in humans (Crettaz et al., 2013; Gibbons et al., 2012; Kuehl et al., 2010; Rhudy and Meagher, 2000), and rodents (Andre et al., 2005; Bardin et al., 2009; Dina et al., 2011; Khasar et al., 2009; Le Roy et al., 2011; Quintero et al., 2011). Furthermore, it is widely documented that stress exacerbates existing pain associated with chronic pain disorders. Thus, stress is an important etiological factor for chronic pain disorders such as shoulder/neck pain syndrome, complex regional pain syndrome and fibromyalgia (Van Houdenhove and Luyten, 2006; Davis et al., 2011; Nilsen et al., 2007; Grande et al., 2004). These findings lend credence to the concept of SIH as a clinically relevant phenomenon, manifesting in a diverse array of stress-related pain disorders including inflammatory bowel disease, fibromyalgia and complex regional pain syndrome (Aaron and Buchwald, 2003; Egle and van Houdenhove, 2006; Grande et al., 2004; Walker et al., 2012). However, fewer studies have investigated the neurobiological mechanisms underpinning SIH.

A particular area of clinical interest within the context of stress-pain interactions is the comorbidity between chronic pain and affective disorders. The findings from numerous studies indicate a very high prevalence of comorbid chronic pain and psychiatric disorders such as anxiety and depression (Asmundson and Katz, 2009; Bair et al., 2003). Chronic pain patients are more likely to present with depression (21.7% vs. 10.0%) or anxiety disorders (35.1% vs. 18.1%) when compared to the general population (McWilliams et al., 2003). The prevalence of clinical anxiety among the population with chronic pain may be as high as 60%, with generalised anxiety disorder being the anxiety disorder that is most prevalent with chronic pain (Fishbain et al., 1986). The co-occurrence of anxiety and/or depression with chronic pain amplifies the negative effects of each alone, often complicating the treatment and resulting in poor outcome (Asmundson and Katz, 2009; Bair et al., 2003; Lieb et al., 2007). The relationship between altered emotional states and chronic pain disorders is complex and it is difficult to establish whether chronic pain leads to altered emotional states or whether the affective disorder predisposes an individual to the development of a pain disorder. For example, it has been reported that 77% of subjects who met criteria for generalised anxiety disorder comorbid with a pain condition, developed the disorder before the onset of chronic pain (Knaster et al., 2011). Taken together, these findings suggest a reciprocal relationship between chronic pain and affective disorders and support the concept of a self-perpetuating cycle of events that may underpin the chronic nature of such comorbid disorders.

In the present manuscript, we aim to provide a comprehensive review and critical analysis of the current understanding of SIH at pre-clinical and clinical levels. The neuroanatomical alterations associated with SIH, as revealed by both studies in human subjects and animal models will be discussed, as will the role of various neurotransmitter and neuromodulatory systems, including the opioidergic, gamma-aminobutyric acid (GABA)ergic, glutamatergic, monoaminergic, endocannabinoid and sympathetic adrenomedullary systems and the hypothalamo-pituitary-adrenal (HPA) axis.

2. Clinical and pre-clinical models of SIH

2.1. Human models

The high prevalence of comorbid psychiatric and chronic pain states, and the reciprocal relationship which they share, suggests the involvement of common neural substrates and mechanisms in the modulation of pain and emotional states. In addition, the current use of drugs such as pregabalin, amitriptyline and duloxetine for the treatment of both pain and anxiety/depression further illustrates the close associations that exist between pain and affective disorders. Increased understanding of common neural substrates and mechanisms is not only important from a fundamental physiological perspective, but may be of potential therapeutic significance. In pursuit of this, a relatively small number of human models employing either psychological or physiological stressors have been developed for studying SIH.

2.1.1. Psychological stress-based models

In general, psychological stress-based models of SIH usually involve assessment of pain responding during or following exposure to a conditioned or unconditioned aversive stimulus.

Please cite this article in press as: Jennings, E.M., et al., Stress-induced hyperalgesia. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.06.003