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Review

A new aspect of chronic pain as a lifestyle-related disease

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ABSTRACT

Physical exercise has been established as a low-cost, safe, and effective way to manage chronic intractable pain. We investigated the underlying mechanisms of exercise-induced hypoalgesia (EIH) using a mouse model of neuropathic pain (NPP). Epigenetic changes in activated microglia and maintained GABA synthesis in the spinal dorsal horn may contribute to EIH. Voluntary exercise (VE), a strong reward for animals, also induced EIH, which may be due in part to the activation of dopamine (DA) neurons in the ventral tegmental area (VTA). VE increases the expression of pCREB in dopaminergic neurons in the VTA, which would enhance dopamine production, and thereby contributes to the activation of the mesolimbic reward system in NPP model mice. We demonstrated that neurons in the laterodorsal tegmental and pedunculopontine tegmental nuclei, a major input source of rewarding stimuli to the VTA, were activated by exercise.

Chronic pain is at least partly attributed to sedentary and inactive lifestyle as indicated by the Fear-avoidance model. Therefore, chronic pain could be recognized as a lifestyle-related disease. Physical activity/inactivity may be determined by genetic/epigenetic and neural factors encoded in our brain. The hypothalamus and reward system is closely related in the axis of food intake, energy metabolism and physical activity. Understanding the interactions between the mesolimbic DA system and the hypothalamus that sense and regulate energy balance is thus of significant importance. For example, proopiomelanocortin neurons and melanocortin 4 receptors may play a role in connecting these two systems. Therefore, in a certain sense, chronic pain and obesity may share common behavioral and neural pathology, i.e. physical inactivity, as a result of inactivation of the mesolimbic DA system. Exercise and increasing physical activity in daily life may be important in treating and preventing chronic pain, a life-style related disease.

Contents

Abbreviations: CBP, chronic low back pain; DA, dopamine; delta FosB, delta FBJ murine osteosarcoma viral; FM, fibromyalgia; GABA, gamma-aminobutyric acid; HDAC, histone deacetylase; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; LHb, lateral habenula; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NPP, neuropathic pain; pCREB, phosphorylated cyclic AMP response element-binding protein; PPTg, pedunculopontine tegmental nucleus; PSL, partial sciatic nerve ligation; RMTg, rostromedial tegmental nucleus; TH, tyrosine hydroxylase; TMD, temporomandibular disorder; VTA, ventral tegmental area; VWR, voluntary wheel running.

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Introduction

Neuropathic pain (NPP) is an intractable form of chronic pain that is produced by damage to and pressure on the peripheral and central nervous systems, and is the most difficult type of pain to treat among chronic pain diseases (Almeida et al., 2015; Jain, 2008). Pharmacological management of NPP has been challenged by clinicians with insufficient outcome. Since only 1025% of patients respond to the first choice drugs for NPP, according to NNT (=number needed to treat) of these drugs (Finnerup et al., 2015), chronic pain patients suffer various side effects of having overdoses of these drugs for long period. On the other hand, non-pharmacological patient-oriented approaches have been proven to significantly attenuate chronic pain. One of those approaches is physical exercise, such as running or swimming. Relevant studies demonstrated that physical exercise in NPP model animals can significantly improve pain-related behaviors, such as mechanical allodynia and heat hyperalgesia (exercise-induced hypoalgesia: EIH) (Kuphal et al., 2007; Shen et al., 2013). However, the underlying mechanisms of how exercise attenuates NPP are not yet well understood. In addition, it is known that physical exercise in clinical patients attenuates their pain symptoms as well, and can appreciably improve their activities of daily living (ADL) (Ambrose and Golightly, 2015; Koltyn et al., 2014). However, exercise therapy is still not actively encouraged to patients with chronic pain because of the uncertainty of the mechanisms underlying EIH. Therefore, understanding these mechanisms will allow a compelling argument to be made for exercise therapy with the goal of improving chronic pain.

Emerging evidence from animal studies has identified several factors that work at different levels of the nervous system as playing critical roles to produce EIH in NPP model animals (Almeida et al., 2015; Bobinski et al., 2015; Chen et al., 2012; Cobianchi et al., 2010, 2013; Kami et al., 2016a, 2016b; Lœpez-êlvarez et al., 2015; Shankarappa et al., 2011; Stagg et al., 2011). A line of research demonstrated that EIH is a hypoalgesia composed of multiple events including marked alterations in inflammatory cytokines, neurotrophins, neurotransmitters, endogenous opioids and histone acetylation in injured peripheral nerves, DRG and spinal dorsal horns in NPP model animals following physical exercise (For review, see Kami et al., 2017). In this review, we introduce our recent findings associated with EIH in NPP model animals and provide a new aspect of chronic pain as a lifestyle-related disease, and then discuss a future direction toward its therapeutic strategy.

Exercise-induced changes in the spinal cord of NPP animals

A line of evidence supports the notion that glial cells in the spinal dorsal horn are key players in the pathogenetic process of NPP (Mika et al., 2013). In line with this notion, some studies showed that treadmill running and swimming in NPP model animals can significantly reduce the expression levels of CD11b, Iba-1 and glial fibrillary acidic protein (GFAP), which are reliable markers for microglia and astrocytes, in the ipsilateral superficial dorsal horn (Cobianchi et al., 2010; Almeida et al., 2015; Lœpez-êlvarez et al., 2015). These results suggest that inactivation of glial cells by physical exercise plays a role in producing EIH. However, our recent study showed that partial sciatic nerve ligation (PSL)-runner mice maintained a markedly increased number of microglia (microgliosis) in spite of attenuation of pain behaviors (Kami et al., 2016a). This discrepancy may be attributed to the different treadmill running protocol used in these studies, suggesting that especially the duration and intensity of treadmill running are important factors in governing analgesic levels of EIH. Also, these results suggest that attenuation of microgliosis in the spinal dorsal horn by physical exercise is not essential in producing EIH.

Recent studies have shown that pharmacological inhibition of histone deacetylases (HDACs) in the spinal cord of NPP model animals improves pain-related behaviors by reducing HDAC1 and enhancing histone acetylation (Cherng et al., 2014; Denk et al., 2013; Kukkar et al., 2014), and have also suggested that epigenetic modification plays an important role in producing and attenuating NPP (Descalzi et al., 2015). Interestingly, intrathecal administration of rat IL-10 protein or intrathecal lentiviral-mediated transfer of IL-10 can reverse the enhanced pain behaviors in CCI model rats (Cianciulli et al., 2015; He et al., 2013). Moreover, it has been shown that epigenetic modification, such as phosphorylation, acetylation and methylation of histone H3 at specific regions in the IL-10 promoter is an important regulatory step for IL-10 production in myeloid cells, including macrophages (Leng and Denkers, 2009; Zhang et al., 2006). These results suggest that epigenetic modifications in activated microglia in the spinal dorsal horn participates in producing EIH, perhaps via the up-regulation of analgesic factors, including IL-10. Our recent study showed that PSL-surgery markedly increased the number of $HDAC1^{+}/CD11b^{+}$ microglia in the ipsilateral superficial dorsal horn, while the number significantly decreased with treadmill running. Moreover, the number of microglia with nuclear expression of acetylated histone H3K9 (H3K9ace) in the ipsilateral superficial dorsal horn remained at low levels in PSL-sedentary mice, but running exercise significantly increased it (Kami et al., 2016a). Thus, our results indicate that the epigenetic modification that causes hyperacetylation of histone H3K9 in activated microglia plays a role in producing EIH. A reasonable explanation for our results may involve the up-regulation of analgesic factors, perhaps IL-10, in the activated microglia. This is the first evidence to our knowledge showing that epigenetic mechanisms are possibly involved in the EIH.

Gamma-aminobutyric acid (GABA) is the principal inhibitory transmitter in the central nervous system, including the spinal dorsal horn. GABA is synthesized from glutamate by glutamic acid decarboxylase (GAD). Two distinct isoforms of GAD, GAD65 and GAD67, have been identified, with each isoform being encoded by separate genes, namely *Gad2* and *Gad1* (Erlander et al., 1991). A line of studies indicated that the functional loss of GABA and/or GADs, especially GAD65, in the spinal dorsal horn contributes to the development of NPP via reductions in the GABA inhibitory tone (Castro-Lopes et al., 1993; Lorenzo et al., 2014; Moore et al., 2002; Vaysse et al., 2011). Our recent study showed that exacerbated pain behaviors following PSL surgery were significantly reduced by treadmill running, and PSL-induced reductions in GAD65/67 production in the superficial dorsal horn were prevented by treadmill running after the PSL surgery, leading to the retention of GABA in interneurons and neuropils. Positive correlations were also observed between the thresholds of pain behaviors and GABA and GAD65/67 levels or GABAergic interneuron numbers in the ipsilateral dorsal horn of PSL-sedentary and runner mice (Kami et al., 2016b). We further demonstrated that the reduction of GAD65, but not GAD67, is selectively prevented by exercise (Kami et al., unpublished observation). Therefore, our results demonstrated that EIH is achieved, at least in part, by the retention of GABAergic inhibition in the spinal dorsal horn. On the other hand, GADs at the protein and mRNA levels are present in the rostral ventromedial medulla (RVM), and these GABAergic RVM neurons massively project into the spinal dorsal horn (Hossaini et al., 2012; Morgan et al., 2008; Pedersen et al., 2011). These GABAergic RVM neurons were also shown to participate in pain inhibition (Zhang et al., 2011). Therefore, GABAergic neurons in the RVM may also be involved in the generation of EIH.