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Invited review

The dichotomized role for acid sensing ion channels in musculoskeletal pain and inflammation

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ABSTRACT

Chronic muscle pain affects between 11 and 24% of the world's population with the majority of people experiencing musculoskeletal pain at some time in their life. Acid sensing ion channels (ASICs) are important sensors of modest decreases in extracellular pH that occur within the physiological range. These decreases in extracellular pH occur in response to inflammation, fatiguing exercise, and ischemia. Further, injection of acidic saline into muscle produces enhanced nociceptive behaviors in animals and pain in human subjects. Of the different types of ASICs, ASIC3 and ASIC1 have been implicated in transmission of nociceptive information from the musculoskeletal system. The current review will provide an overview of the evidence for ASIC3 and ASIC1 in musculoskeletal pain in both inflammatory and non-inflammatory models.

This article is part of a Special Issue entitled 'ASIC Channels'.

1. Introduction

Chronic muscle pain affects between 11 and 24% of the world's population with the majority of people experiencing musculoskeletal pain at some time in their life (Committee on Advancing Pain Research CaEIoM, 2011). In the U.S. alone, such chronic pain is estimated to have an economic burden of over $600 billion dollars annually (Committee on Advancing Pain Research CaEIoM, 2011; Gaskin and Richard, 2012). Pain of the musculoskeletal system is associated with reduced function and significant disability. Musculoskeletal pain can occur as a direct result of injury and is associated with injury and inflammation. Some inflammatory conditions persist, such as rheumatoid arthritis, and lead to long-lasting pain and disability. In most cases the acute injury resolves, but in some cases pain persists despite the lack of peripheral tissue injury or inflammation. Treatment of the pain associated with inflammatory and non-inflammatory pain may differ and depend on knowledge of the underlying mechanisms.

Non-inflammatory pain conditions include chronic widespread pain conditions such as fibromyalgia as well as more localized pain conditions such as non-specific neck and back pain or temporomandibular disorder. These conditions are commonly associated with muscle tenderness, resting pain, pain with movement, and significant disability without detectable tissue damage. On the other hand conditions such as osteoarthritis have clear peripheral joint degradation and synovial inflammation. However, often times the evidence of tissue damage does not match the pain and there is a wide variability in pain and disability (Sluka et al., 2012). Further, inflammatory arthritis conditions such as rheumatoid arthritis have clear joint inflammation that is associated with pain. Again the pain is variable and does not often match the extent of inflammation or joint destruction. Indeed, it is generally accepted that while peripheral nociceptors are critical to the development and maintenance of a variety of pain conditions, that there are central nervous system changes that may underlie some of the variability. Thus, there are a variety of different musculoskeletal pain conditions that each have a unique pathobiology that includes a role for nociceptors at the site of insult that can subsequently alter central nociceptive pathways.

Acid sensing ion channels (ASICs) are important sensors of decreases in extracellular pH (Waldmann et al., 1997) that occur within the physiological range. Of the different types of ASICs, ASIC3 and ASIC1 have been implicated in transmission of nociceptive information from the musculoskeletal system (Sluka et al., 2009). ASIC3 is found in primary afferent fibers innervating

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muscle and joint (Molliver et al., 2005; Ikeuchi et al., 2009, 2008; Sluka et al., 2003a), including those expressing markers found in nociceptive afferents, e.g. substance P and calcitonin gene-related peptide (Molliver et al., 2005; Ikeuchi et al., 2009, 2008; Price et al., 2001) (Fig. 2). ASIC1 is also found in primary afferent fibers that express nociceptive markers and has been implicated in nociceptive processing in the peripheral and central nervous system (Sluka et al., 2009; Olson et al., 1998). ASICs form heteromers in vivo, and dorsal root ganglia neurons (DRG) express both ASIC1 and ASIC3 (Benson et al., 2002; Gautam and Benson, 2013). In DRG innervating muscle, decreases in pH produce inward ASIC-like currents (Gautam et al., 2010, 2012) and application of acidic solutions activates group IV unmyelinated muscle afferent fibers (Hoheisel et al., 2004). Further, injection of acidic saline into muscle produces enhanced nociceptive behaviors in animals (Price et al., 2001; Sluka et al., 2001). Similarly, in human subjects, infusion of acidic buffer into the tibialis anterior tibialis muscle of the leg results in local pain at the site of infusion and referred pain at the ankle. In addition, these subjects report a decrease in pressure pain thresholds at both the site of infusion (primary hyperalgesia) and at the ankle (secondary hyperalgesia) (Frey Law et al., 2008) (Fig. 1). In human subjects, decreases in pH occur in inflammatory conditions, in myofascial pain, and after fatiguing exercise (Goldie and Nachemson, 1969, 1970; Shah et al., 2005; Hood et al., 1988). These decreases in pH would be expected to activate ASICs on primary afferent fibers to produce pain. The current review will provide an overview of the evidence for ASIC3 and ASIC1 in musculoskeletal pain in both inflammatory and non-inflammatory models.

2. ASICs in non-inflammatory pain

To model non-inflammatory pain, our laboratory developed a model of persistent hyperalgesia without overt tissue damage (Gautam et al., 2012; Sluka et al., 2001; Gregory et al., 2013a). This model is induced by two injections of acidic saline into one muscle, 5 days apart. Hyperalgesia develops within hours at the site of injection, but also occurs at remote sites in the contralateral muscle,

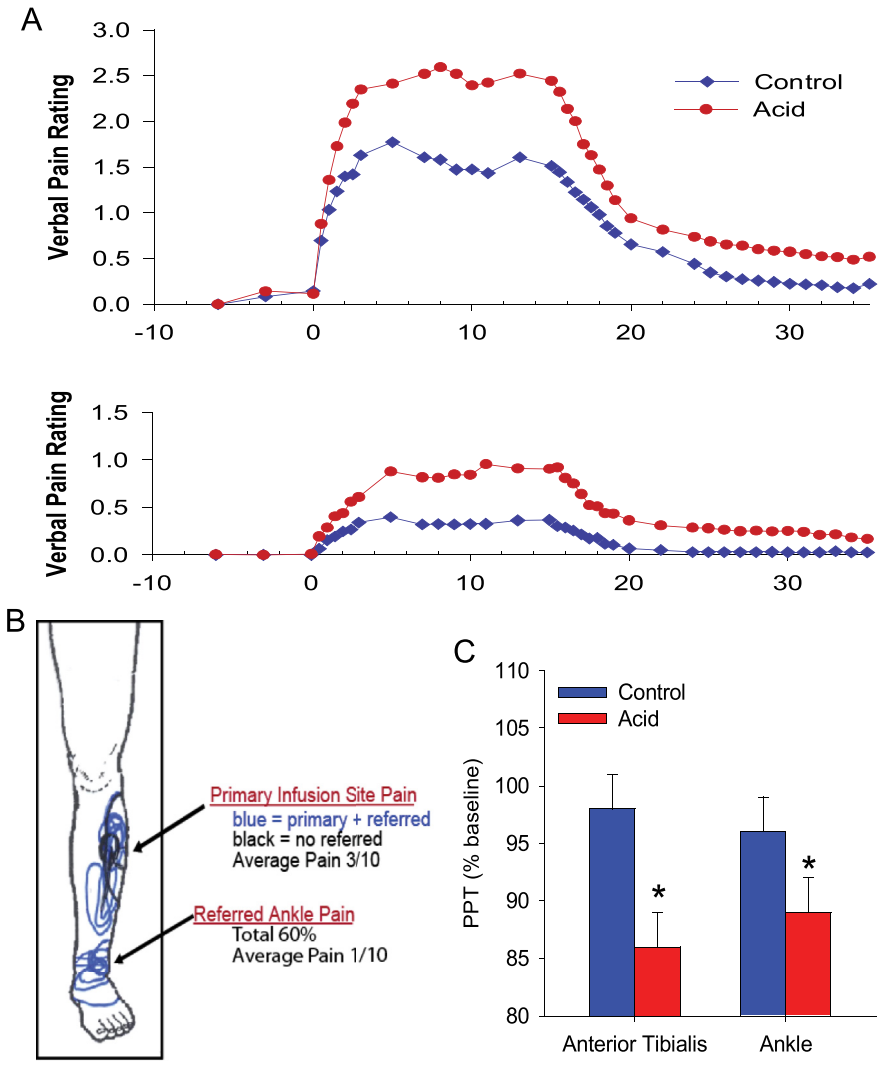

Fig. 1. This figure shows data from human subjects where pH 5.2 acidic buffer was infused into the tibialis anterior muscle and compared to saline controls. The infusion was started at time 9 and continued for 15 min. Pain ratings at the site of infusion and in the referred pain site (A), drawings of area pain felt by subject (B) and pressure pain thresholds at the site of infusion and in the referred pain site (C) were measured. **A**. Pain intensity ratings in the group infused with acidic buffer averaged around 2.5–3.0/10 during the infusion for the primary site of pain, and about 1/10 in the referred pain site at the ankle. **B**. The primary pain site occurred at the infusion site. A portion of the subjects, approximately 60%, had pain referred to the ankle, while 40% had only localized pain. **C**. Pain thresholds were significantly decreased from baseline during infusion of acidic buffer at both the site of infusion, primary hyperalgesia, and in the referred pain site, secondary hyperalgesia. Figures and data were redrawn from Frey Law et al. (2008).

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