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Inter-individual responses to experimental muscle pain: Baseline anxiety ratings and attitudes to pain do not determine the direction of the sympathetic response to tonic muscle pain in humans

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ABSTRACT

We have recently shown that intramuscular infusion of hypertonic saline, causing pain lasting ~60 min, increases muscle sympathetic nerve activity (MSNA) in one group of subjects, yet decreases it in another. Across subjects these divergent sympathetic responses to long-lasting muscle pain are consistent over time and cannot be foreseen on the basis of baseline MSNA, blood pressure, heart rate or sex. We predicted that differences in anxiety or attitudes to pain may account for these differences. Psychometric measures were assessed prior to the induction of pain using the State and Trait Anxiety Inventory (STAI), Pain Vigilance and Awareness Questionnaire (PVAQ), Pain Anxiety Symptoms Scale (PASS) and Pain Catastrophising Scale (PCS); PCS was also administered after the experiment. MSNA was recorded from the common peroneal nerve, before and during a 45-minute intramuscular infusion of hypertonic saline solution into the tibialis anterior muscle of 66 awake human subjects. Forty-one subjects showed an increase in mean burst amplitude of MSNA (172.8 ± 10.6%) while 25 showed a decrease (69.9 ± 3.8%). None of the measured psychological parameters showed significant differences between the increasing and the decreasing groups. We conclude that inter-individual anxiety or pain attitudes do not determine whether MSNA increases or decreases during long-lasting experimental muscle pain in healthy human subjects.

1. Introduction

Similar to the sensory aspects of pain – superficial pain being perceived as sharp or burning, and deep pain as dull and aching (Henderson et al., 2006) – the cardiovascular responses to noxious inputs vary according to the tissue of origin. In 1942, it was shown that superficial pain (arising from skin) resulted in an increased pulse rate, whereas pain that arose from deeper structures (muscle) showed a decrease in pulse rate and blood pressure (Lewis, 1942). Feinstein and colleagues confirmed these findings in 1954, when they found that muscle pain was associated with a fall in blood pressure, as well as bradycardia, in awake human subjects (Feinstein et al., 1954).

1.1. Pain and sympathetic nerve activity

Over the past few years we have been using intramuscular as well as subcutaneous injections of hypertonic saline to examine the effects of deep and superficial pain on muscle sympathetic nerve activity (MSNA) in awake human subjects (Burton et al., 2009a). Interestingly, it was shown that both types of pain – when hypertonic saline was injected as a bolus – caused an increase in MSNA (Burton et al., 2009a), and a transient increase in skin sympathetic nerve activity (SSNA) (Burton et al., 2009b). These results support previous findings of increased cardiovascular responses to deep and superficial pain in animals (Horeyseck and Jänig, 1974; Sato et al., 1984; Boczek-Funcke et al., 1992).

In more recent studies we have used intramuscular *infusion* of hypertonic saline to produce a sustained, steady-state level of pain (Fazalbhoy et al., 2012, 2014; Hall et al., 2012). This continuous nociceptive input has been shown to produce a transient increase in skin sympathetic nerve activity (SSNA) followed by a sustained decrease in all subjects (Hall et al., 2012), yet divergent muscle sympathetic responses: half of the subjects experienced a sustained increase in MSNA, blood pressure and heart rate during tonic muscle pain, while the other half showed sustained decreases (Fazalbhoy et al., 2012, 2014; Kobuch et al., 2015). Moreover, the direction of the sympathetic response to tonic muscle pain was reproducible (Fazalbhoy et al., 2014). That is, subjects who had an increase in MSNA, blood pressure, and heart rate during the first session showed a similar response in a subsequent session, conducted weeks apart. This consistency was also true for the

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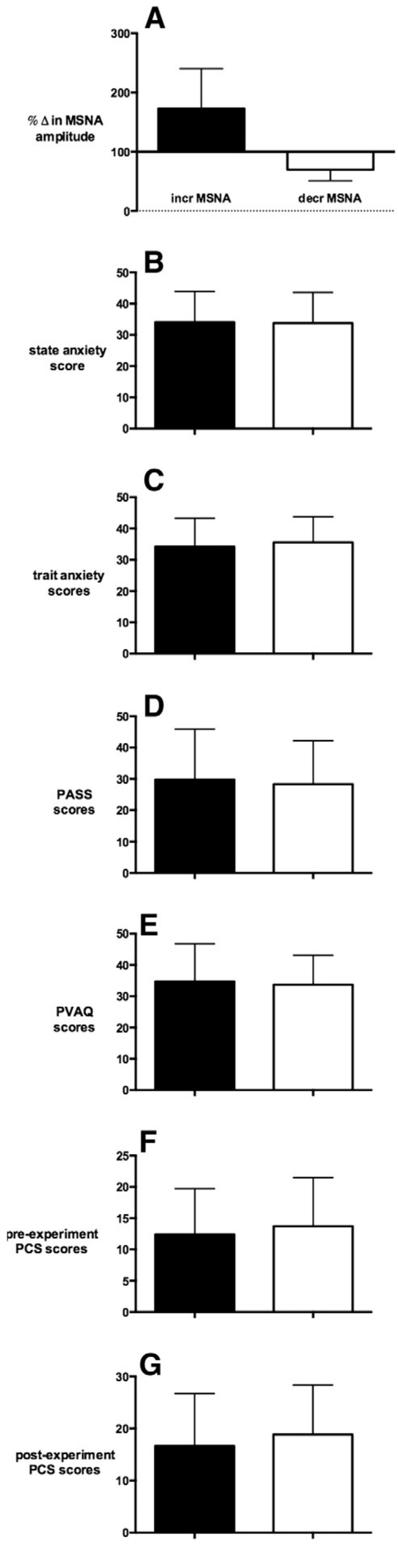

Fig. 1. Anxiety and attitudes to pain scores for the increasing and decreasing MSNA groups. Changes in MSNA amplitude (A), state anxiety scores (B), trait anxiety scores (C), PASS scores (D), PVAQ scores (E), pre-experiment PCS scores (F), and post-experiment PCS scores (G) for each group.

subjects experiencing a fall in MSNA. We recently showed that the divergent muscle sympathetic responses to muscle pain cannot be explained by sex or by differences in resting blood pressure, heart rate, heart rate variability or MSNA (Kobuch et al., 2015).

So, we are left with trying to understand why these two divergent patterns of sympathetic response to long-lasting muscle pain come about. Here, we posit that psychological differences may account for the different physiological responses. In particular, given that increases in sympathetic nerve activity are features of the fight or flight response to a threatening stimulus, we speculate that subjects showing higher anxiety levels, or greater negative attitudes to pain, will show increases in MSNA during tonic muscle pain, while those who are better able to cope do not.

1.2. Negative emotions and pain

Catastrophising – "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" (Sullivan et al., 2001) – has been associated with increased distress and higher pain ratings during painful interventions (Chaves and Brown, 1987; Spanos et al., 1979; Sullivan et al., 2006). Parallel increases in catastrophic thinking and intensity of pain (Carter et al., 2002; Sullivan et al., 2006), as well as severity of depression and anxiety (Keefe et al., 1989; Martin et al., 1996), have also been observed. Accordingly, one might expect that subjects with high catastrophising scores would exhibit greater sympathetic responses to pain.

1.3. Anxiety and MSNA

It is well known that patients with anxiety have an elevated cardiovascular risk (Musselman et al., 1998; Rosengren et al., 2004). Metabolic syndrome patients with anxiety and mood disorders have greater MSNA burst frequency at rest, compared to metabolic syndrome patients and controls without these psychological symptoms (Toschi-Dias et al., 2013). Moreover, single unit recordings from muscle vasoconstrictor neurones in metabolic syndrome patients with high blood pressure revealed a higher incidence of multiple firing during a burst when levels of anxiety were high (Lambert et al., 2010). This disturbed sympathetic firing pattern was also found in patients with panic disorder and major depressive disorder (Lambert et al., 2006, 2008). Other indirect measures of sympathetic activity, such as pulse transit time (Richards and Bertram, 2000) and catecholamine levels (Villacres et al., 1987), have also been shown to reflect higher sympathetic nerve activity - with higher levels of anxiety in healthy participants and panic disorder patients. Therefore, we might expect that anxious subjects would show an increase in sympathetic activity during pain.

Given the above, in the current study we administered questionnaires to subjects before and after an intramuscular infusion of hypertonic saline to test the hypothesis that elevated levels of anxiety, and/or negative attitudes to pain, leads to a higher prevalence of increases than decreases in MSNA during tonic muscle pain.

2. Methods

Experiments were carried out on 66 healthy subjects (27 females, 39 males), aged 18 to 39 years. All subjects provided written informed consent to the experimental procedures, which were conducted under the approval of the Human Research Ethics Committee of Western Sydney University and satisfied the requirements of the Declaration of Helsinki. No subject had any history of cardiovascular disease, chronic musculoskeletal pain, or mental health disorders.