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Sex-specific effects of intranasal oxytocin on thermal pain perception: A randomised, double-blind, placebo-controlled cross-over study

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ABSTRACT

Chronic neck and shoulder pain (CNSP) is a common musculoskeletal disorder in adults, which is linked to hypersensitivity to noxious stimuli. The hormone oxytocin has been implicated as a potential therapeutic for the management of chronic pain disorders, and has been suggested to have sex-specific effects on the salience of threatening stimuli. This study investigated the influence of intranasal oxytocin on the perception of noxious thermal stimuli. Participants were 24 individuals with CNSP lasting > 12 months (eight women), and 24 age- and sex-matched healthy, pain-free controls. In a randomised double-blind, placebo-controlled, cross-over study, participants attended two sessions, self-administering intranasal oxytocin (24 IU) in one session, and placebo in another. Participants rated intensity and unpleasantness of thermal heat stimuli at three body sites: the cervical spine, deltoid, and tibialis anterior, on 11-point numerical rating scales. Compared with placebo, intranasal oxytocin increased the perceived intensity of noxious heat stimuli in women with CNSP (Cohen's d = 0.71), but not in men with CNSP, or healthy, pain-free controls. Men and women displayed divergent sensitivity across target sites for ratings of pain intensity (partial eta squared = 0.12) and pain unpleasantness (partial eta squared = 0.24), irrespective of drug condition. Men were more sensitive at the cervical spine and deltoid, whereas women were more sensitive at the tibialis. These findings suggest that oxytocin and endogenous sex hormones may interact to influence the salience of noxious stimuli. The hyperalgesic effects of oxytocin in women suggest that caution should be taken when considering oxytocin in the management of chronic pain.
Trial Registration: CT-2016-CTN-01313-1; ACTRN12616000532404

1. Introduction

Chronic musculoskeletal neck-shoulder pain (CNSP) is a common disorder in working adults, with an estimated prevalence of 30–50% (Cote et al., 2009). Chronic pain in this body region has a significant impact on quality of life (Rezai et al., 2009) and causes substantial disability (Hoy et al., 2014). Families of those with CNSP are also impacted due to the physical and emotional changes associated with this chronic pain condition (West et al., 2012). In addition to the health and psychosocial burden of CNSP, there is a significant financial burden of CNSP due to sick leave and lost productivity (e.g., Hagberg et al., 2007). Persons with CNSP display hypersensitivity to noxious and innocuous stimuli, including reduced pain thresholds to experimental stimuli compared to controls (Van Oosterwijck et al., 2013), suggesting the presence of dysregulation in the processing of ascending nociceptive signals. However, these findings are inconsistent across studies (Coronado et al., 2014; Scott et al., 2005; Uthaikhup et al., 2015). A wide spectrum of interventions are used for the treatment of CNSP (e.g., surgery, opioid medications). Many of these treatments, however, have limited effectiveness, and are associated with increased risk of hyperalgesia (MacDermid et al., 2009). There is a clear need to develop novel effective treatments for CNSP.

Recent evidence suggests that the neuropeptide oxytocin decreases sensitivity to experimentally-induced pain in humans and animals that are otherwise pain-free (Rash et al., 2014). Consequently, oxytocin has been suggested as a potential treatment for chronic pain conditions (Tracy et al., 2015). Oxytocin is a peptide hormone produced within the

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nuclei of the hypothalamus (Sofroniew and Weindl, 1981) that is released into the peripheral circulation via the posterior pituitary gland (Carter et al., 2007; Uvnas-Moberg and Petersson, 2004). Traditionally, oxytocin is known for its peripheral actions involving contractions of uterine muscles during childbirth (Dale, 1906) and the "letdown reflex" during lactation (Ruis et al., 1981). However, there is also an extensive distribution of oxytocin receptors throughout the brain (especially in regions such as the anterior cingulate cortex, periaqueductal grey, and amygdala; MacDonald and MacDonald, 2010). Oxytocin has been shown to have a range of effects throughout the central nervous system. For instance, oxytocin has been implicated as a key regulator of social cognition and behaviour (Heinrichs et al., 2009), especially the processing of the salience of social and emotional information (Bartz et al., 2011; Shamay-Tsoory and Abu-Akel, 2016).

Sex-specific effects of intranasal oxytocin administration are evident, such that after intranasal oxytocin amygdala activation in response to presentation of fear-evoking stimuli is decreased in men (Kirsch et al., 2005), but increased in women (Domes et al., 2010). Whether these sex differences apply in relation to pain experience is not known. This is because previous studies have either examined the effects of oxytocin only in male rodents (e.g., Yang et al., 2011), and many studies in humans only recruited men (Paloyelis et al., 2016; Singer et al., 2008; Zunhammer et al., 2015), or if they recruited both men and women, they failed to analyse the data with respect to sex (Rash and Campbell, 2014). Therefore, while oxytocin seems to have a hypoalgesic effect, it remains unknown whether these effects are sex-specific, or if they occur in persons with chronic pain.

There are several potential mechanisms through which oxytocin may exert analgesic effects. One such mechanism is a direct hypothalamo-spinal projection from the paraventricular nucleus of the hypothalamus (a major site of endogenous oxytocin production) to the dorsal horn of the spinal cord (Gimpl and Fahrenholz, 2001), an area involved in the modulation of pain. Within the dorsal horn, there is a subset of neurons containing oxytocin receptors that influence glutamatergic neurons. These glutamatergic neurons, in turn, activate GABAergic neurons, leading to inhibition of pain-signalling A-delta (Aδ-) and C-fibers (e.g., Condes-Lara et al., 2009). A second potential mechanism involves the relationship between oxytocin and the endogenous opioid system (Han and Yu, 2009). In a rodent study, administration of oxytocin to the periaqueductal grey, which contains an opioid system that controls descending pathways that prevent pain signals traveling along the spinal cord (Melzack and Wall, 1988), resulted in reduced sensitivity to pain (Yang et al., 2011). These effects were subsequently blocked by the administration of an opioid receptor antagonist, thus highlighting their likely interactions with the opioid system within the periaqueductal grey.

Regardless of the exact mechanism, there is moderate evidence to suggest that oxytocin exerts analgesic effects. The strongest of this evidence comes from the animal literature, where 90% of the 33 studies included in a recent systematic review reported strong evidence for analgesic effects of oxytocin in response to acute, experimentally-induced pain (Rash et al., 2014). Importantly, 23 of these studies only tested male animals, three studies only tested female animals, and the remaining studies did not specify the sex of the animals. Testing was usually limited to males to avoid variability in behaviour thought to accompany the oestrous cycle (Ochedalski et al., 2007). Despite prominent effects in these preclinical studies, the evaluation of analgesic effects of intranasal oxytocin in humans have yielded mixed results. Rash and Campbell (2014) reported that intranasal oxytocin reduced behavioural and physiological reactions in response to cold-pressor pain in young, pain-free men and women. Zunhammer et al. (2015) reported that intranasal oxytocin reduced subjective pain intensity ratings in response to the delivery of thermal heat stimuli in pain-free men, but there was no effect on thermal heat pain thresholds. In contrast, Singer et al. (2008) reported no effect of intranasal oxytocin on the unpleasantness of experimentally-induced electrical pain in healthy, pain-free men (intensity ratings were not collected). Only a handful of studies have investigated the analgesic effect of intranasal oxytocin in persons with chronic pain, including fibromyalgia (Mameli et al., 2014), and irritable bowel syndrome (Ohlsson et al., 2005), but failed to observe any analgesic effects. To date, no studies have examined the potential analgesic effects of intranasal oxytocin in individuals with CNSP, and whether the effects of oxytocin vary in comparison with persons who don't have chronic pain, or between men and women.

The current study was designed to investigate the differences in sensitivity to noxious thermal heat pain stimuli across the body in individuals with CNSP and healthy, pain-free controls. We hypothesised that (1) individuals with CNSP would provide higher ratings of pain intensity and pain unpleasantness in comparison to healthy, pain-free controls, particularly at sites proximal to their chronic pain (i.e., the cervical spine), (2) that intranasal oxytocin would decrease the sensitivity to pain in both groups, compared to placebo, and (3) that intranasal oxytocin, compared to placebo, would increase sensitivity to noxious thermal heat stimuli in women, but decrease sensitivity to noxious stimuli in men.

2. Methods

2.1. Study design

This study employed a randomised, double-blind, placebo-controlled cross-over design adhering to CONSORT guidelines (Moher et al., 2012). Each participant was tested under two acute treatment conditions separated by a washout period of at least 14 days (mean days between testing sessions = 16.3; range = 14–36). There are several advantages to this design. First, there is a reduction in the influence of potential extraneous confounding factors (e.g., age and sex of participants), as each participant is tested under both conditions. Second, there is higher statistical power compared to a between-subjects design, so that the required sample size to detect meaningful effects is smaller (Senn, 2002). Potential participants were screened for eligibility and randomised (as per procedures described in 2.4.1, below) to complete the experimental protocol by author LMT.

The protocol was approved by the Monash University Human Research (CF15/659–2015000303) and the Alfred Human Research (111/16) Ethics Committees and followed the Helsinki Declaration of 1975. The study was registered with the Australian Government Therapeutic Goods Administration under the Clinical Trial Notification scheme (protocol number CT-2016-CTN-01313-1) and the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au; registration number ACTRN12616000532404).

We aimed to recruit 25 participants with CNSP, and 25 age- and sex-matched healthy, pain-free, controls, providing a total sample size of 50. This target was set following power analysis via G*Power, in which we estimated small-medium effects with 80% power and alpha of 0.05 (Faul et al., 2007). This sample size was consistent with that used in prior research studies on pain (e.g., Rash and Campbell, 2014; Scott et al., 2005), and allowed for participant attrition of 10% and data loss as a result of technical failures and other unforeseen circumstances.

2.2. Study setting

Volunteers with CNSP were recruited via local private physiotherapy clinics, and online advertising between September 2015 and December 2016. Data collection ceased once the a priori defined sample size had been recruited. All participants gave written, informed consent and received $120 AU for their participation. Participants were free to withdraw their consent at any point during the study. The two testing sessions were always scheduled to commence between 9:00 am and 10:30 am, to prevent excessive diurnal variation in hormonal levels (Brondino et al., 2017). Participants were greeted by a male experimenter, who guided them through the experimental tasks. Participants