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Intranasal oxytocin reduces heart rate variability during a mental arithmetic task: A randomised, double-blind, placebo-controlled cross-over study

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ABSTRACT

Heart rate variability (HRV) refers to variation in the interval between successive heart beats. Low HRV is an indicator of potential autonomic nervous system dysfunction. People with chronic pain often display autonomic dysregulation, especially in the parasympathetic nervous system. The hormone oxytocin has been shown to increase HRV in non-clinical samples, but its potential impact on HRV in persons with chronic pain is unknown. This study investigated the impact of intranasal oxytocin on HRV in persons with chronic neck and shoulder pain. Participants included 24 individuals with chronic neck and shoulder pain lasting > 12 months and 24 age- and sex-matched pain-free controls. In a randomised double-blind, placebo-controlled, cross-over study, participants self-administered intranasal oxytocin (24 IU) in one session, and placebo in another, before HRV was recorded at rest and during a mental arithmetic task. Intranasal oxytocin did not influence HRV at rest. However, compared to placebo, intranasal oxytocin elicited small decreases in low-frequency and high-frequency HRV in both groups during the mental arithmetic task. These results suggest that intranasal oxytocin may enhance the salience of the mental arithmetic task, leading to reduced engagement of the parasympathetic nervous system when completing the task. Further investigation and replication of these findings are required to improve our understanding of the effects of intranasal oxytocin on autonomic functioning both at rest and under cognitive stress.

1. Introduction

Chronic neck and shoulder pain (CNSP) affects 30 to 50% of adults (Cote et al., 2009; Manchikanti et al., 2009). There is evidence suggesting that individuals affected by CNSP display an imbalance between the sympathetic and parasympathetic nervous systems (Hallman et al., 2011). Imbalances between the sympathetic and parasympathetic nervous systems can be visualised through heart rate variability (HRV), which refers to the variability in the interval between successive heartbeats. High levels of variability indicate a highly adaptable nervous system that is able to regulate emotional and behavioural responses to threatening internal and external stimuli (Appelhans and Luecken, 2006; Friedman and Thayer, 1998). In contrast, low levels of variability are associated with a plethora of poor long-term health outcomes, such as cardiovascular disease and mood disorders (Appelhans and Luecken, 2006), and chronic pain (Koenig et al., 2016; Tracy et al., 2016). Persons with chronic pain have reduced HRV, compared to persons without chronic pain, particularly with respect to high-frequency HRV (HF-HRV; Koenig et al., 2016; Tracy et al., 2016). Therefore, reducing autonomic dysregulation (i.e., improving HRV) in persons with chronic pain is important, as doing so may have widespread implications for the health and wellbeing of these individuals.

When at rest, the parasympathetic nervous system exerts tonic inhibitory dominance over the sympathetic nervous system. Parasympathetic modulation of the heart is faster acting than sympathetic modulation (Levy, 1997), with the majority of parasympathetic control exerted via the vagus nerve (Porges et al., 1994). Therefore, HF-HRV has been proposed as a surrogate measure of vagal activity (Koenig et al., 2015). Reductions in vagally-mediated HRV have been associated with excessive worry, difficulties in emotion regulation, psychiatric illness, and cardiovascular disease

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(e.g., Chalmers et al., 2014, 2016; Geisler et al., 2013; Thayer et al., 2010; Williams et al., 2015).

Oxytocin is a neuropeptide that has been found to modulate HRV in some non-clinical studies, when administered intranasally and compared with placebo (Kemp et al., 2012; Norman et al., 2011). This nine amino acid neuropeptide is predominantly produced within the nuclei of the hypothalamus (Gimpl and Fahrenholz, 2001). Although oxytocin is more commonly known for binding to oxytocin receptors located in the uterine muscle, causing contractions of the uterine muscles to initiate childbirth (Fuchs et al., 1982), oxytocin can also bind to oxytocin receptors distributed throughout the central nervous system (Gimpl and Fahrenholz, 2001). Consequently, oxytocin binds to receptors in brain regions such as the hypothalamus and amygdala, which are involved in the control of autonomic activity (Benarroch, 2001, 2006). Stimulation of oxytocin neurons has been reported to induce bradycardia, and lead to increases in vagal tone (Higa et al., 2002; Rogers and Hermann, 1986). Furthermore, oxytocin neurons display increased activation during stressful events, thereby serving to alleviate psychophysiological stress responses by lowering heart rate via increased vagal tone (Higa et al., 2002).

Intranasal oxytocin does not only appear to increase HRV at rest in non-clinical samples (Kemp et al., 2012; Norman et al., 2011), it has also been found to increase calmness and reduce anxiety during the socio-evaluative Trier Social Stress Test (Heinrichs et al., 2003). Moreover, neuroimaging studies have shown that intranasal oxytocin restores normal amygdala and prefrontal activity (Labuschagne et al., 2010, 2012), including amygdala connectivity with prefrontal regions (Dodhia et al., 2014; Gorka et al., 2015) in persons with social anxiety. These regions also play a key role in the regulation of autonomic functioning (Benarroch, 2001, 2006). Taken together, previous research provides converging evidence to suggest that oxytocin may increase HRV at rest, and may enhance the engagement of parasympathetic inhibition of arousal in response to mild stressors. Specifically, oxytocin may mechanistically increase HRV in persons with chronic pain given their demonstrated parasympathetic dysregulation.

To date, no studies have investigated the effects of intranasal oxytocin on HRV in persons with chronic pain. The current study therefore investigated whether an acute dose of intranasal oxytocin could increase HRV in persons with CNSP at rest, and during a mental arithmetic task (i.e., by reducing the stress response). We hypothesised that persons with CNSP would display reduced HRV at rest and during a mental arithmetic task, compared to persons who were pain-free. We also hypothesised that intranasal oxytocin, compared to placebo, would increase HRV in persons with CNSP and pain-free persons.

2. Methods

Twenty-four volunteers with constant CNSP lasting > 12 months (eight women) were recruited from private physiotherapy clinics and the wider community, along with 24 age- and sex-matched pain-free controls, between September 2015 and December 2016. The study was designed as a randomised double-blind placebo-controlled cross-over study where each participant was tested under two acute treatment conditions (i.e., 24 international units (IU) of intranasal oxytocin, or an intranasal placebo) separated by a period of at least 14 days. The duration of this period was set at a minimum of 14 days to minimise potential practice or learning effects between the two testing sessions for the tasks participants completed throughout the sessions (e.g., on the mental arithmetic task). Details of participant screening and recruitment are reported elsewhere (Tracy et al., 2017a). All participants gave written, informed consent prior to commencing the study, and received $120AU for their participation. All data were collected in a behavioural research laboratory at Monash University.

The study aimed to investigate the effects of intranasal oxytocin on the modulation of pain-related experiences in persons with CNSP. A series of tasks were completed to examine the effects of intranasal oxytocin on HRV, physical functioning, thermal heat pain thresholds, sensitivity to experimentally-induced pain, and the anticipation and experience of thermal heat stimuli. The tasks relating to HRV are the focus of the current paper. As such, only methods relating specifically to the experimental tasks relevant to this paper will be described herein. Information relating to the design and protocol of the whole study is available online (Tracy et al., 2017a). The results of the tasks not analysed for this paper is discussed elsewhere (e.g., Tracy et al., 2017b). This 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. This study was registered with the Australian Government Therapeutic Goods Administration under the Clinical Trials Notification Scheme (protocol number CT-2016-CTN-01313-1) and the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au; registration number ACTRN12616000532404).

2.1. Procedure

Upon arrival, participants completed questionnaires relating to demographic information (age, sex, medication use, education, etc.), mood (Beck Anxiety Inventory-I and Beck Depression Inventory-II; Beck and Steer, 1990; Beck et al., 1996), pain (Brief Pain Inventory; Cleeland and Ryan, 1994), and the severity of symptoms associated with their neck and shoulder injuries (Symptom Intensity Rating Scale; Davidson and De Nardis, 2011). Participants then self-administered a nasal spray of either oxytocin or placebo as per the randomisation schedule. After a waiting period of 45 min, participants commenced the experimental tasks. The experimental tasks described in this paper were conducted on average 45 min post-intranasal oxytocin administration. To ensure a standardised experience while waiting for drug absorption, additional demographic data (i.e., height and weight) were collected from participants and the remaining time was spent watching documentaries that had been screened for neutral content for approximately 40 min. The electrophysiological recording equipment was then attached and the experimental tasks commenced.

2.2. Physiological recording and processing

This study used an 8/35 PowerLab unit (AD Instruments, Sydney, Australia) for continuous measurement of heart rate (HR). A five-lead electrocardiogram (ECG) system was used with disposable, pre-gelled electrodes (diameter 35 mm, Coviden) placed in the following pattern: one beneath the lower right clavicle, one beneath the lower left clavicle, one on the lower right ribs, one on the lower left ribs, and one approximately halfway down the sternum, slightly to the right of the midline. The tasks examining HRV did not commence until a clear and accurate ECG recording was obtained. The ECG R-R series were obtained by the identification of a local maximum after crossing the threshold of the derivative series via dedicated software (HRV Module, LabChart, AD Instruments). All relevant segments were visually inspected and corrected for false or undetected R-waves and ectopic beats. Undetected R-waves were manually inserted, and ectopic beats were excluded from analysis. The raw ECG signal was filtered with a 0.3 to 20 Hz band-pass filter, sampled at a rate of 2000 Hz, before being smoothed with a Savitzky-Golay filter (window width 155 samples) and undergoing a Fast Fourier Transformation using Welch's Periodogram (window width 1024s, 50% overlap). HR data were extracted offline using LabChart Pro version 7.3.7 software (AD Instruments, Sydney, Australia).

Both time- and frequency-domain measures of HRV were extracted from the ECG recordings. *Time-domain measures* focus either on the heart rate at any given time, or on the intervals between successive normal intervals (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).