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Intranasal oxytocin in the treatment of anorexia nervosa: Randomized controlled trial during re-feeding

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ABSTRACT

Background: Nutritional rehabilitation in anorexia nervosa (AN) is impeded by fear of food, eating and change leading to treatment resistance. Oxytocin (OT) exerts prosocial effects and modulates trust, fear, anxiety and neuroplasticity. The current placebo-controlled RCT examined the effects of intranasal oxytocin (IN-OT) in AN. The aim was to ascertain whether repeated doses of IN-OT enhance treatment outcomes in AN.

Methods: AN patients self-administered 36 IU IN-OT or placebo daily for 4–6 weeks during hospital treatment. The outcome measures were change in the Eating Disorders Examination (EDE) scale, weight gain, cognitive rigidity, social anxiety, obsessive and autistic symptoms. The effects of the first and last doses of IN-OT were assessed relative to placebo before and after a high-energy afternoon snack, to determine potential dampening of cortisol and anxiety levels by OT.

Results: Weight gain was similar in both groups. The EDE eating concern subscale score was significantly lower after IN-OT treatment as was cognitive rigidity. There were no significant differences in social anxiety or any of the other outcomes at follow-up. After four weeks IN-OT, salivary cortisol levels were significantly lowered in anticipation of an afternoon snack compared to placebo. Morning plasma OT levels did not change after chronic IN-OT or with weight restoration.

Conclusion: IN-OT might enhance nutritional rehabilitation in AN by reducing eating concern and cognitive rigidity. Lower salivary cortisol levels in response to IN-OT suggest diminished neuroendocrine stress responsiveness to food and eating. Such effects require replication with inclusion of more sensitive subjective measures.

1. Introduction

Anorexia nervosa (AN) is a serious public health problem with one of the highest mortality rates and treatment costs of any psychiatric disorder (Arcelus et al., 2011). With an average duration of 7 years and full recovery rates of only 50%, many patients suffer chronically, imposing a heavy burden on their families and the health system (Klump et al., 2009). AN is characterised by ritualistic and repetitive behaviours around control of nourishment in the service of self-worth (Russell, 2013) usually with important developmental and genetic underpinnings. Advances in treatment for AN have stalled in recent years (Bulik et al., 2007) and currently there is no one drug or psychotherapy that is more effective in treating AN than supervised refeeding (Hay et al., 2014). Efficacy of weight restoration early on has been shown to influence later recovery, so improving the whole process of nutritional rehabilitation is an obvious target for improving treatment outcomes (Lund et al., 2009).

Oxytocin (OT) is a nonapeptide and neuromodulator produced by the paraventricular and supraoptic nuclei of the hypothalamus. It is released into the bloodstream via the portal circulation of the posterior pituitary where it is stored, as well as directly into the limbic system where it binds to OT receptors (Gimpl and Fahrenholz, 2001). Thus, OT acts as both a hormone and a neuropeptide. OT is found exclusively in mammals and modulates many functions including learning, memory,

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food consumption, stress and anxiety, reproductive and social behaviours, trust, drug reward and social bond formation (Maguire et al., 2013; McGregor et al., 2008).

The strongest evidence for a therapeutic role of OT is in Autistic Spectrum Disorder (ASD) where OT has been shown to reduce both the number and the types of core autistic repetitive behaviours, e.g. ordering, compulsion to tell/ask and touching (Bakermans-Kranenburg and van IJzendoorn, 2013; Hollander et al., 2003). Adolescents with ASD performed better on emotion recognition tasks when treated with OT (Guastella et al., 2015) and in adults with ASD, OT produced higher liking and trusting of a friendly stranger (Andari et al., 2010). However, these findings have not as yet been shown to translate into clinical efficacy in terms of behavioural management of ASD (Guastella et al., 2015).

Similar to autism, AN is an illness marked by repetitive and rigid behaviours, high anxiety, social deficits and withdrawal (Oldershaw et al., 2011) and several lines of evidence suggest OT may be therapeutically beneficial. First, cerebrospinal fluid levels of OT and overnight secretion of OT are reduced in patients with AN (Demitrack et al., 1990). Second, OT secretion is blunted in response to stimuli such as oestradiol and hypoglycemia in low weight AN and this recovers following weight gain (Chiodera et al., 1991). More recently, Fetissov et al. (2005) suggested that the derangement of the OT system might underlie elevated anxiety and social deficits in AN. Nocturnal levels of pooled serum OT in women with AN are considerably reduced relative to healthy women (Lawson et al., 2011). Subsequent reports (Lawson et al., 2012, 2013) found abnormal postprandial serum OT in AN even after recovery and that morning basal levels of plasma OT were lower in AN subjects compared to healthy women, or those with bulimia nervosa (Monteleone et al., 2016b). Kim et al. (2014) have shown that single doses of IN-OT attenuate attentional bias to food-related cues in AN patients and that this might contribute to a reduction of eating concern and other food focussed fear and anxiety based psychopathology.

The primary aim of the current study was to ascertain whether IN-OT improves inpatient nutritional rehabilitation outcomes in AN patients relative to placebo. Our exploratory analysis investigated potential beneficial effects of chronic OT administration on weight gain, core eating disorder psychopathology, autism-spectrum features, social anxiety, identification of emotional expression, obsessive-compulsive features, motivation to change, stage of illness, and cognitive flexibility.

A secondary aim was to establish whether a subset of participants receiving repeated dosing of IN-OT would demonstrate a dampening of anxiety levels and salivary cortisol response in anticipation of consuming a high-energy snack on the first and last dose of the trial. Previous research suggests high levels of pre-meal anxiety in AN patients (Steinglass et al., 2010). Moreover, underweight AN patients show elevated basal salivary cortisol levels relative to healthy controls (Monteleone et al., 2016a) suggesting a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. IN-OT can dampen salivary cortisol responses to various stressors, especially in clinical populations (Cardoso et al., 2014). Thus, we predicted that IN-OT might dampen cortisol and stress-related effects associated with consumption of a high-energy snack. Such snacks are normally avoided by those with AN and this provocation test provides a test of the capacity of oxytocin to modulate stress in response to food stimuli.

2. Material and methods

2.1. Study design and participants

The current study was a pilot randomised controlled trial assessing the feasibility, safety, acceptability and efficacy of IN-OT during hospital-based nutritional rehabilitation in patients with AN. Participants provided written informed consent prior to participation and parental consent was obtained for those under 18 years of age. Ethical approval for this study was granted by the local area Ethics Committee (RPAH) and Ramsay Health Ethics Committee overseeing Northside Clinic.

Female inpatients who met DSM-IV diagnostic criteria for AN aged between 16 and 60 years were eligible. Patients were recruited from the residential Eating Disorders Unit at Northside Clinic, Greenwich Sydney, Australia over two time periods: Dec. 2011 to May 2012 (study 1) and May 2013 to Dec. 2013 (Pilot study 2). DSM-IV diagnoses of AN restricting or binge/purging subtype and other comorbid diagnoses were confirmed by consensus for clinical data obtained from the Structured Clinical Interview for DSM (SCID-I), the treating psychiatrist, Eating Disorder Examination (EDE) (Fairburn et al., 2008) and Clinician Administered Staging Instrument for Anorexia Nervosa (C-ASIAN) (Maguire et al., 2012).

The exclusion criteria were age less than 16 years, male, a body mass index (BMI) of 19·5 kg/m^2 or more, IQ < 80 on a measure of verbal IQ, currently pregnant, current manic episode or psychosis, alcohol or drug dependence, acute suicidality, severe medical comorbidity (e.g. epilepsy, cancer or diabetes), major septal deviation or previous nasal condition, or involuntary patients currently under the Mental Health Act. Patients taking psychiatric medications were included and remained on these over the course of the trial as per clinical need. Medications included antidepressants for comorbid depression and low dose atypical second generation antipsychotic agents (olanzapine or quetiapine) to reduce anorexic preoccupations and improve sleep.

2.2. Randomisation, masking and sample size

Participants who consented to participate were randomly allocated (1:1) to receive OT or placebo plus usual nutritional rehabilitation care. Allocation was done using computer randomization. A randomization list was provided to the compounding chemist formulating the OT and placebo nasal sprays, who was then responsible for treatment allocations. Nasal sprays were packaged and labeled with an ID number from the trial pharmacy. Only the trial pharmacist and compounding chemists were aware of treatment condition: participants, investigators, assessors, hospital and other trial staff were masked to treatment assignment. On completion, Pilot 2 patients were asked which treatment arm they thought they received to assess whether the blinding was effective.

Pilot study 1 was an exploratory study to determine the potential benefits of OT on a range of outcome measures and to infer treatment effect size. Based on an interim analysis, EDE eating concern improved more in the OT group (Mean placebo −0.27, OT −1.51, SD = 1.19). Using a standard power calculation of 80% power and alpha set at 0.05, the number required for a two-tailed test is approximately 30 subjects (15 in each arm).

Pilot study 2 was conducted to recruit the extra subjects to ensure sufficient power for the planned analysis using the EDE eating concern as the primary outcome measure. In order to reduce drop-outs and ensure compliance, the length of trial was shortened from 6 weeks (Pilot 1) to 4 weeks (Pilot 2) and all nasal spray doses were conducted as inpatients under nurse supervision. Two of the outcome measures from Pilot 1 (the Brixton Activation and the Stroop tasks) were dropped in Pilot 2 as these did not change over time in Pilot 1 for either group and overlapped with other measures that were retained.

2.3. Oxytocin nasal spray

IN−OT and placebo treatment sprays were commercially produced by Stenlake Compounding Chemist in Sydney (Bondi, NSW). The OT spray comprised OT in addition to glycerol, sorbitol, benzyl alcohol and distilled water that was contained in an amber 7 mL glass nasal spray with a metered pump. Matched placebo sprays were identical in composition, but contained no OT. Each pump spray delivered 50 μL of OT (9 IU) or placebo. For patients in Pilot study 1 who received a 6 week course, a second nasal spray was supplied when necessary. All sprays