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The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa

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ABSTRACT

Background: Anorexia nervosa (AN) is characterised by severe malnutrition as well as intense fear and anxiety around food and eating with associated anomalies in information processing. Previous studies have found that the neuropeptide, oxytocin, can influence eating behaviour, lower the neurobiological stress response and anxiety among clinical populations, and alter attentional processing of food and eating related images in AN.
Methodology: Thirty adult women with AN and twenty-nine healthy comparison (HC) women took part in the current study. The study used double blind, placebo controlled, crossover design to investigate the effects of a single dose of intranasal oxytocin (40 IU) on a standard laboratory smoothie challenge, and on salivary cortisol, anxiety, and attentional bias towards food images before and after the smoothie challenge in AN and HC participants. Attentional bias was assessed using a visual probe task.
Results: Relative to placebo intranasal oxytocin reduced salivary cortisol and altered anomalies in attentional bias towards food images in the AN group only. The oxytocin-induced reduction in attentional avoidance of food images correlated with oxytocin induced reduction in salivary cortisol in the AN group before the smoothie challenge. Intranasal oxytocin did not significantly alter subjective feelings of anxiety or intake during the smoothie challenge in the AN or HC groups.
Conclusions: Intranasal oxytocin may moderate the automated information processing biases in AN and reduce neurobiological stress. Further investigation of the effects of repeated administration of oxytocin on these processes as well as on eating behaviour and subjective anxiety would be of interest.

1. Introduction

Anorexia nervosa (AN) is characterised by an intense fear of food and eating with associated avoidance behaviours and severe malnourishment (American Psychiatric Association, 2013). Over time these associations become stronger and cues related to food and eating become linked to changes in brain function and information processing biases begin to develop (Schmidt and Treasure, 2006; Treasure et al., 2012; Yackobovitch-Gavan et al., 2009). To date, a number of studies have demonstrated that relative to healthy individuals, people with AN have elevated plasma and salivary cortisol levels, which suggests a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Bailer and Kaye, 2003; Connan et al., 2003; Lawson et al., 2013b; Licinio et al., 1996). Furthermore, behavioural studies have found that people with AN have elevated autonomic responses to illness-related stimuli, such as food (Léonard et al., 1998; Rigaud et al., 2007; Soussignan et al., 2011; Uher et al., 2004). A study investigating the effect of a blind gastric load of 0, 300, or 700 calories on endocrine responses in AN found that the cortisol response increased with the calorie content of the gastric load in the AN participants (Rigaud et al., 2007). Further work has also demonstrated that relative to healthy participants, people with AN report greater fear and disgust in response to food stimuli, and have elevated corrugator facial EMG (i.e. frowning) and physiological arousal response to food images and when confronted

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with a test meal (Léonard et al., 1998; Soussignan et al., 2011; Uher et al., 2004).

In addition to elevated anxiety and stress around eating, people with AN also have anomalies in attention towards food (Brooks et al., 2011). A meta-analysis found that people with AN show an increased attentional bias (AB) towards food images (Brooks et al., 2011). Another study utilising eye-tracking methodology found that relative to healthy participants, people with AN showed early AB towards food images, but later avoidance of food images (Giel et al., 2011). Similarly, electroencephalogram (EEG) and magnetoencephalography (MEG) studies have found elevated early and reduced later posterior activation in people with AN compared to healthy individuals in response to food stimuli (Godier et al., 2016; Wolz et al., 2015). Interestingly, a study by Cardi et al. (2013) investigated AB towards food images before and after a standard test meal challenge and found that inpatients with AN showed greater AB towards food images following exposure to a test meal challenge. Thus, taken together, these findings suggest that anomalies in AB towards food images is a prominent feature of AN and is likely fuelled by stress and anxiety around food and eating.

Animal studies have demonstrated that the neuropeptide oxytocin is involved in many regulatory functions in the central nervous system including stress response and food intake (Cochran et al., 2013; Olszewski et al., 2010). A recent meta-analysis found that intranasal oxytocin significantly reduced cortisol response to stressful stimuli among clinical populations of people suffering from a range of disorders, including depression, substance dependence, fragile X syndrome and borderline personality disorder, characterised by a chronic dysregulated and hyperactivated HPA axis (Cardoso et al., 2014). Additionally, emerging evidence from animal studies has demonstrated that central administration of an oxytocin receptor agonist can normalise novelty-induced decrease in food intake in mice, suggesting that oxytocin may play a role in moderating the influence of stress and anxiety on eating (Olszewski et al., 2014). Thus intranasal oxytocin may be helpful facilitating exposure treatment for food restriction fuelled by anxiety.

There has been increasing interest in the possibility that oxytocin may be involved in the pathophysiology of eating disorders (Maguire et al., 2013). A recent meta-analysis reported that peripheral and cerebrospinal fluid (CSF) levels of endogenous oxytocin were significantly lower in AN relative to normal weight controls, which the authors suggested is likely associated with dysregulation of the HPA axis (Rutigliano et al., 2016). Additionally, another study has reported atypical, elevated oxytocin response to food intake in AN, which was associated with pre-meal hypoactivation of the hypothalamus, orbitofrontal cortex, insula, and amygdala in response to food images in AN relative to healthy participants (Lawson et al., 2013b; Lawson et al., 2012). Moreover, a recent proof of concept study found that a single dose of 40IU of intranasal oxytocin reduced anomalies in AB towards images of food, eating, and negative body shape in people with AN (Kim et al., 2014a). The authors also found that intranasal oxytocin led to a reduction in caloric intake in the 24 h following administration in participants with bulimia nervosa (Kim et al., 2015). These findings suggest that intranasal oxytocin can alter anomalies in attentional processes to specific and general aversive stimuli in AN and may alter eating behaviour.

The aim of the current study was to examine the impact of a single dose of intranasal oxytocin on a standard smoothie challenge, as well as neurobiological stress and AB towards food images, as measured with a visual probe task, before and after the smoothie challenge in adult women with AN and gender and age matched healthy control (HC) participants. Based on previous findings outlined above, we hypothesised that relative to HCs, participants with AN would consume less during the smoothie challenge, have elevated anxiety and salivary cortisol, and anomalies in AB towards food images before and after the smoothie challenge. Additionally, we hypothesised that oxytocin administration would decrease anxiety, increase smoothie intake, reduce cortisol and alter anomalies in AB towards food images in participants with AN.

2. Methods and materials

2.1. Participants

Fifty-nine women participated in the study. Thirty women met the DSM-5 criteria for AN, with mean BMI of 16.30 (SD = 2.04) and age of 26.20 (SD = 6.82). Diagnosis was confirmed using the Structured Clinical Interview for DSM-5 (First et al., 2015). Fifteen of the AN participants were recruited from the South London and Maudsley NHS Foundation Trust inpatient unit and were in treatment. The other fifteen AN participants were recruited through ED charities (BEAT, Succeed). Fifteen of the AN participants were taking medication (anti-depressants) during the study.

The HC participants (N = 29), with mean BMI of 23.25 (SD = 3.65) and age of 26.83 (SD = 8.54), were recruited from the community and amongst King's College London students and staff. HC participants were of normal weight and were screened for current or past psychiatric disorders, and alcohol or drug misuse with the Structured Clinical Interview for DSM-5 (First et al., 2015). Participants were excluded from the study if they reported medical or psychiatric problems, a history of or current alcohol or drug abuse, current impairments in cardiovascular functioning, pregnancy or plans to become pregnant during the study. Prior to participating in the study, all participants gave a written informed consent. Ethical approval for the study was obtained from National Research Ethics Service (NRES) committee (14/LO/0128) and all procedures were conducted in accordance with the latest declaration of Helsinki (2008).

The sample size was based on power analysis conducted with G*Power for a repeated measures design (Faul et al., 2007). To ensure adequate power (0.80) to detect an effect in the mixed model, the total recommended sample size was 60 participants.

2.2. Experimental design

The study employed a double blind, placebo controlled, within subjects, crossover design. All participants received a single dose of both oxytocin and placebo in separate sessions. The treatment order was pseudo-randomised so that half of the AN participants and half of the HC participants received oxytocin in the first session and the other half of the AN and HC participants received oxytocin in the second session. Only the Maudsley pharmacy, responsible for dispensing the compounds were aware of the order in which each participant received the compounds. The experimenter and the participants were both blind to treatment order.

The study flow chart is presented in Supplementary Fig. S1 . Prior to administration of the compounds participants were asked to provide a saliva sample for cortisol analysis, and to provide a baseline rating of anxiety on a visual analogue scale (VAS) (for further details see Supplementary information). The intranasal oxytocin and the placebo were self-administered by the participants in ten sprays, five sprays in each nostril every 45 s (for further details see Supplementary information). Fifty minutes after administration, participants gave the second saliva sample and VAS anxiety rating. The first visual probe task was then administered approximately 55 min after administration of the compound (T1; for further details see Supplementary information). This was followed by the smoothie challenge consisting of a 250 ml fruit smoothie (a choice from 3 Innocent smoothie flavours: strawberries and bananas, mangoes and passion fruits, and kiwis, apples and limes).