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Short Communication

Effects of intranasal oxytocin on the attentional bias to emotional stimuli in patients with bulimia nervosa

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Highlights for review

- Dysregulated social perception is a possible causative factor for interpersonal difficulties in BN
- Oxytocin inhibits the amygdala response to threat and modulates emotional reactivity
- BN shows a similar increase in attentional processes to anger as the healthy comparison group
- Intranasal oxytocin reduced the attentional bias to anger in both BN and the healthy

comparison group

Abstract

Background: Bulimia nervosa (BN) is characterized by binge eating and emotional dysregulation including increased negative affectivity (anger, anxiety). The aim of this study was to examine the effect of oxytocin on attentional processes towards anger in patients with BN.

Method: The study design consisted of a double-blind, placebo-controlled within-subject crossover, single dose experiment. Sixty-four women (31 patients with BN and 33 healthy comparisons) completed self-reported measures to evaluate emotional difficulties and were administered a single dose of intranasal oxytocin (40IU) or placebo followed by a visual probe detection task to examine attentional orienting to angry or happy faces.

Results: Patients with BN reported higher emotional dysregulation and more difficulties in controlling anger compared to the healthy comparison group. Patients with BN and the healthy women exhibited similar attentional bias to angry faces in the placebo condition. Intranasal oxytocin reduced the attentional bias towards angry faces in both the BN patients and the healthy women.

Conclusions: We found that a single dose of oxytocin reduced vigilance towards angry faces in patients with BN as well as healthy women. The results showed that patients with BN are not different from healthy women in terms of vigilance towards threat.

Keyword: oxytocin, bulimia nervosa, anger, emotional regulation, attentional bias

1. Introduction

A recent maintenance model of bulimia nervosa (BN) has proposed that elevated impulsivity,

sensitivity to punishment, and interpersonal difficulties reduce the rewarding aspects of social interaction (Treasure et al., 2018). This in turn is believed to feed into increased emotion dysregulation, shame, and information processing biases, leading to greater reliance on eating as a coping mechanism and source of reward. The model is supported by findings that people with BN show increased attention and sensitivity towards negative social cues (Caglar-Nazali et al., 2014; Cardi et al., 2014; Cardi et al., 2013). Observational studies have also reported that binge eating episodes are frequently preceded by negative affect, especially anger and interpersonal distress (Haedt-Matt and Keel, 2011). Moreover, experimental studies have found that people with BN are characterized by a high propensity to express anger inadequately (Krug et al., 2008), which can lead to binge eating through impulsive emotional dysregulation (Amianto et al., 2012). Furthermore the trajectory of improvement in emotional regulation associated with treatment varies between eating disorders with the most change found in BN (Mallorqui-Bague et al., 2018).

Oxytocin, a neuropeptide, has a central role in neural circuits involved in social behaviour, appetite, anxiety, and stress. Previous work has suggested that oxytocin plays an important role in regulating social cognition by altering amygdala and prefrontal reactivity to social cues (Guastella and MacLeod, 2012; Ross and Young, 2009). Improvements in emotion recognition and theory of mind, and increased attention towards positive social cues following intranasal oxytocin among healthy people (Bakermans-Kranenburg and van, 2013; Domes et al., 2013; Macdonald and Macdonald, 2010). Oxytocin might contribute to the etiology of eating disorders, and social cognition is one of these pathways (Giel et al., 2018). Our pilot study found intranasal oxytocin similarly improved emotion recognition sensitivity in BN and healthy people (Kim et al., 2015), which suggested that reactivity to emotional stimuli may be a greater source of difficulties in BN and therefore, examining the effects of oxytocin in this area would be of interest.

The aim of the study was to build on existing literature and examine the impact of a single dose of intranasal oxytocin on attentional bias towards emotional cues in BN. As anger in particular is believed to play an important role in the maintenance of disordered eating in BN, we were interested in examining the impact of intranasal oxytocin on attentional reactivity to angry in addition to happy and neutral faces. Our first hypothesis was that patients with BN would show increased attention to

angry faces due to sensitivity towards negative social cues. Our second hypothesis was that oxytocin would reduce attentional bias towards anger and increase the bias towards positive and neutral faces in BN.

2. Materials and methods

2.1. Participants

Sixty-four young women [31 patients with BN and 33 healthy comparisons (HC)] took part in this study. Patients with BN were recruited from the outpatient clinic of Eating Disorders Clinic at Seoul Paik Hospital, Seoul, South Korea. The BN diagnosis was confirmed using a Structured Clinical Interview (First et al., 2007) based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The exclusion criteria for patients were as follows: active substance use disorder and psychotic disorder. Those who had other comorbidities were allowed. In the sample, the common psychiatric comorbid disorders were depressive disorders (n=13), anxiety disorders (n=8) and borderline personality disorder (n=7) based on DSM-5. Other than the 7 patients who were taking fluoxetine, patients who were taking psychiatric medications were excluded.

The HC participants were students from the women's university in Seoul, South Korea. The inclusion criteria were healthy females without a history of medical or psychiatric illnesses, not taking regular medication including the contraceptive pill, and a minimum age of 17 years. The exclusion criteria were as follows: self-reported history of psychiatric, developmental, or neurological disorders, and substance dependence.

The sample size was based on an a priori power analysis conducted with G*Power (Faul et al., 2007), which indicated a minimum sample size of 60 (power = 0.8) to detect significant effects. All participants provided written informed consent prior to participating in the study. The study protocol was approved by both the Korean Food and Drug Association Institutional Review Board (approval number: 12061) and the Institutional Review Board of Seoul Paik Hospital (approval number: IIT-2012-096). This study was registered with the Clinical Research Information Service (http://cris.nih.go.kr) (registration number: KCT0000716).

2.2. Experimental design

We applied a double-blind, placebo-controlled, within subjects, crossover design. The preparation methods for the oxytocin and placebo are shown in Supplementary Information 1. Participants without amenorrhea (n = 61) were tested during the follicular phase of their menstrual cycle (approximately days 3 through 12). All participants received a single dose of both oxytocin (40 IU per dose) and placebo in separate sessions in accordance with current guidelines (Carson et al., 2013). Each participant visited the laboratory twice for testing: once for the placebo condition and once for the oxytocin condition. The order of the placebo or oxytocin administration for each participant was determined randomly by a project coordinator who was not involved in the experiment. The visual probe detection task commenced 45 minutes after the intranasal administration of oxytocin or placebo. For further details please see Supplementary Information 2.

2.3. Measurements

2.3.1. Self-reported psychometric assessments

All participants completed self-reported measures to evaluate emotional difficulties and eating disorders psychopathology. For further details please see Supplementary Information 3.

2.3.2. Visual probe detection task

A visual probe detection task was used to measure attentional biases. The stimuli consisted of happy (n = 15), angry (n = 15), and neutral (n = 15) facial expressions of 15 adults were selected from 2 databases of Korean facial expressions of emotion (Lee et al., 2013; Park et al., 2011). An emotional and a neutral face were presented simultaneously, side by side on a screen followed by a probe either at the target's location (emotional face) or at the distractor's location (neutral face). A fixation cross was displayed at the centre of the screen for 750 ms followed by the target and non-target stimuli pair for 1,000 ms. The reaction time (RT) was measured from the onset of the visual probe following the prime until the button press. For further details please see Supplementary Information 4.

2.4. Statistical analysis

We followed a standard analytical procedure for the visual probe detection task (Bradley et al., 1999). Only RTs from trials in which probes were correctly identified were included in the analysis. The correct response rates were 99.9% for the BN group and 99.7% for the HC group. Mean RTs were calculated for each participant, and the outlier trials were removed by excluding detection latencies beyond two standard deviations from their mean (i.e., from each individual's mean RTs across all stimuli).

Attentional bias (AB) was calculated for each matched trial type (happy-neutral, angry-neutral) by subtracting the mean RT for probes replacing the emotional prime from the mean RT for probes replacing the neutral prime. A positive AB indicated increased attention for the emotional prime while a negative AB indicated attention away from the emotional prime. The AB data were analyzed by a 2x2x2 mixed linear model using SPSS 23 (SPSS Inc., Chicago, IL, USA). The drugs (oxytocin and placebo), emotions (happy and angry), and groups (BN and HC) were entered as fixed effects while the subjects were the random effect. Multiple models were built to evaluate the model fit based on variance-covariance structures. Based on the results from the 2 Log Likelihood, the Akaike Information Criterion, and the Schwarz Bayesian Criterion, final models with a diagonal structure were reported (Littell et al., 2000). The significant interactions were post hoc tested with simple effects tests, and the effect sizes for independent and dependent t-tests are reported using Cohen's *d*. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the participants are summarized in Table 1. Ages, body mass indexes (BMI, kg/m^2), and IQ levels were not significantly different among the patients with BN and the HC participants.

(Table 1. Clinical characteristics of patients with bulimia nervosa and the healthy comparisons)

3.2. Attentional bias to anger/happy expression faces

The AB scores among the BN and HC groups following oxytocin and placebo administration are presented in Table 2. The mixed model revealed no effects from the Drug x Emotion x Group interaction [$F(1,228.082) = 0.002$, $p = 0.965$] or Emotion [$F(1,228.082) = 0.136$, $p = 0.712$] on the AB scores. However, there were effects from the Drug x Emotion interactions [$F(1,228.082) = 6.413$, $p = 0.012$] and Drug [$F(1,228.082) = 6.118$, $p = 0.014$] on the AB scores. Oxytocin significantly reduced the AB towards angry faces in both the patients with BN and HC participants. A simple effect test showed that the AB to angry faces was reduced by oxytocin [$F(1,120.632) = 10.217$, $p = 0.002$] whereas the AB to happy faces was not [$F(1,118.034) = 0.002$, $p = 0.962$]. Figure S1 for AB scores is presented in Supplementary Information 5. In addition, we explored whether oxytocin induced changes in the AB scores correlated with psychometric variables or not. The results are shown in Supplementary Information 6 and 7, and further investigation was not carried out as there were no differences in AB between the BN and HC groups.

(Table 2. Attentional bias scores (in ms) towards angry and happy faces in the visual probe task for the oxytocin or placebo sessions in patients with bulimia nervosa and the healthy comparisons)

4. Discussion

The aim of this study was to examine the effect of intranasal oxytocin on the attentional reactivity to anger in patients with BN. The findings revealed that relative to the HC group, the BN participants did not show greater AB towards anger in the placebo condition. Instead, both groups showed similar vigilance towards the angry faces, which was attenuated by intranasal oxytocin.

The present findings are supported by previous findings reporting positive impact of intranasal oxytocin on social cognition and cooperation among healthy individuals (Bakermans-Kranenburg and van, 2013; Domes et al., 2013; Macdonald and Macdonald, 2010). Moreover, findings from our previous work also showed that oxytocin similarly improved sensitivity to recognize basic emotions

among the BN and HC participants (Kim et al., 2015). Therefore, taken together these findings suggest that intranasal oxytocin may have a generally positive impact on social-emotional processing.

In the context of the maintenance model of BN (Treasure et al., 2018), the present findings are encouraging that intranasal oxytocin could help to reduce elevated sensitivity to negative social cues, which in turn could help to alleviate information processing biases. Thus, ultimately intranasal oxytocin could potentially help to break the loop in BN. However, it is of importance to note that the present study did not find a group difference in AB towards anger or on the effects of oxytocin on AB. Thus, research with larger sample size may be needed to explore this possibility further.

In this study, taking fluoxetine was accepted as an inclusion criterion. Although, it is a common clinical practice for treating BN, it might be confounding the effect of oxytocin on AB as SSRIs may modify specific neural dysfunctions correlated to negative cognitive biases (Di Simplicio et al., 2012). Therefore, the effect of fluoxetine on oxytocin and AB needs to be investigated in a further study.

The main limitation of the present study was the relatively small sample size, which prevented further exploration of the potential confounding effects of individual differences, including childhood trauma and comorbid diagnoses. Additionally, a recent meta-analysis reported that the visual probe task may not be optimal for measuring AB and recommended that future studies should opt for more sensitive measures to examine the effects of oxytocin in AB (Leppanen et al., 2018). Third, the comorbid psychiatric disorders might influence the effect of oxytocin and AB. Finally, as the study was carried with a Korean sample, the study needs to be replicated for other racial ethnic populations to determine the generalizability of the findings.

In conclusion, patients with BN show similar increased attention to threat stimuli, and similar moderation effects with oxytocin as found in healthy comparison group.

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or writing of this report. The corresponding author has full access to all of the data in this study and has final responsibility for the decision to submit for publication.

Author contributions

YK and JT were involved with the study design. YK conducted the data collection and JE conducted the data analysis. YK, JT, JL, and ML were involved with the interpretation of results and the preparation of the draft article. All authors read and gave their approval of the final version of the article.

Conflicts of interests

There are no conflicts of interest for all authors.

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Figures

Table 1. Clinical characteristics of patients with bulimia nervosa and the healthy comparisons

Characteristics	BN (N=31)	HC (N=33)	*t*	*p*	*d*
Age, years	23.87(3.99)	22.45(2.22)	1.76	0.082	0.42
Age of onset, years	19.90(4.72)	NA	NA	NA	NA
BMI, kg/m^2	20.79(2.62)	20.85(2.40)	-0.08	0.932	0.02
Intelligence	106.44(13.79)	111.20(6.28)	-1.69	0.096	0.44
EDE-Q					
Restraint	2.1(1.76)	0.87(0.86)	3.53	0.001	0.89
Eating Concern	2.77(1.67)	0.60(0.77)	6.56	<0.001	1.68
Shape Concern	3.50(1.58)	1.68(1.11)	5.25	<0.001	1.34
Weight Concern	4.04(1.46)	2.44(1.20)	4.72	<0.001	1.20
Global	3.11(1.36)	1.40(0.85)	5.93	<0.001	1.51
BDI	18.52(12.23)	7.58(7.00)	4.31	<0.001	1.09
STAI					
State	53.65(13.16)	43.03(11.52)	3.37	0.001	0.85
Trait	57.81(12.32)	44.03(11.32)	4.58	<0.001	1.16
STAXI					
Anger_State	13.55(7.97)	11.79(4.99)	1.06	0.290	0.26
Anger_Trait	22.06(7.26)	18.73(6.13)	1.99	0.051	0.49
Anger_Supression	19.81(4.85)	17.79(4.27)	1.77	0.082	0.44
Anger_Expression	17.32(4.43)	15.03(3.95)	2.18	0.032	0.54
Anger_Control	19.35(5.35)	19.24(4.92)	0.08	0.930	0.02
DERS					
Non-acceptance	16.42(6.18)	9.82(5.64)	4.46	<0.001	1.11
Goals	17.03(3.71)	13.90(2.91)	3.69	<0.001	0.93
Impulsivity	15.74(5.20)	11.85(5.07)	3.03	0.004	0.75
Awareness	17.65(4.90)	19.68(3.92)	-1.80	0.076	0.45
Strategies	21.68(6.34)	15.16(5.69)	4.25	<0.001	1.08
Clarity	12.65(2.60)	12.97(1.74)	-0.57	0.568	0.14

Data are shown as mean (SD). d = Cohen's d, BN = bulimia nervosa, HC = healthy comparison, BMI = body mass index, EDE-Q = Eating Disorders Examination Questionnaire, BDI = Beck Depression Inventory; STAI-State, Spielberger State and Trait Anxiety Inventory State Score, STAI-Trait = Spielberger State and Trait Anxiety Inventory Trait score, STAXI = State and the Trait Anger Expression Inventory, DERS = Difficulties in Emotion Regulation Scale, Non-acceptance = non-acceptance of emotional responses, Goal = difficulties engaging in goal-directed behaviour, Impulsivity = impulse control difficulties, Awareness = lack of emotional awareness, Strategies = limited access to

emotion regulation strategies, Clarity = lack of emotional clarity, NA = Not applicable

Table 2. Attentional bias scores (in ms) towards angry and happy faces in the visual probe detection task for the oxytocin or placebo sessions in patients with bulimia nervosa and the healthy comparisons

Prime face	BN (n=31)		*t*(*df*=30)	*p*	*d*	HC (n=33)		*t*(*df*=32)	*p*	*d*
	Placebo	Oxytocin				Placebo	Oxytocin			
Happy	10.68(79.96)	9.72(74.34)	0.04	0.967	0.01	11.55(71.99)	13.72(58.35)	-0.14	0.889	-0.03
Angry	40.44(95.34)	-12.10(90.34)	2.67	0.012	0.47	39.76(101.35)	-9.51(74.97)	2.17	0.037	0.37

Data are shown as mean (SD). Analyzed by paired t-test. BN = bulimia nervosa, HC = healthy comparison, *d* = Cohen's *d*.