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ABSTRACT

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Rapid-onset anorectic effects of intranasal oxytocin in young men

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Keywords: Oxytocin; Eating; Appetitive behaviour; Reward

ABSTRACT

Although the neuropeptide oxytocin exhibits many of the characteristics that would support its use as an anorectic agent for overeaters, studies of oxytocin's effectiveness at reducing eating in humans remain limited. In a double-blind, placebo-controlled crossover study, under the pretext of examining oxytocin's effects on various aspects of sensory perception, 20 men were given 24 IU of oxytocin and took a taste test of sweet, salty, and neutral snacks 45 minutes later. Participants self-rated appetite, anxiety, and other mood parameters, and then were left alone for 10 minutes with the pre-weighed snack food and invited to help themselves. To minimize the influence of hunger-driven eating, lunch had been provided immediately after oxytocin administration. In line with Ott et al. (2013), oxytocin significantly reduced the consumption of sweet foods; however, it also reduced consumption of salty snacks. Self-reported anxiety did not differ across drug conditions. The study is the first to demonstrate an effect of oxytocin on snack eating at 45 minutes post administration and on salty snacks. The anorectic efficacy of oxytocin after 45 minutes cannot easily be explained by the same mechanism as the one presumed to underpin its effects in previous studies that adopted much longer intervals between drug administration and testing.

1. INTRODUCTION

Oxytocin is a nonapeptide hormone released from the neurohypophysis centrally and into systemic circulation. The hormone is traditionally associated with the physiology of parturition (Zeeman, Khan-Dawood, & Yusoff Dawood, 1997), but its effects on a wide range of processes have now been recognised, including effects on prosocial behaviour, memory, and anxiety (e.g. Chini, Leonzino, Sala, & Braida, 2014; Tost et al., 2010). Oxytocin receptors have been identified in areas of the brain associated with reward, and they interact with dopamine receptors in these regions to alter motivation, including the motivation to eat (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013; Romero-Fernandez, Borroto-Escuela, Agnati, & Fuxe, 2013; Sabatier, Leng, & Menzies, 2013). The anorectic effects of oxytocin have been established in animal models: the peptide acts in the hypothalamus to inhibit appetite (Arletti, Benelli, & Bertolini, 1989; Leng et al., 2008; Maejima et al., 2009) and its effects are reversed by oxytocin antagonists (Arletti et al., 1989; Olson, Drutarosky, Stricker, & Verbalis, 1991; Olson et al., 1991). Oxytocin also reduces rodent preferences for sweet-tasting foods and prevents overconsumption of hyper-palatable food pellets via reward pathways in the limbic system (Amico, Vollmer, Cai, Miedlar, & Rinaman, 2005; Miedlar, Rinaman, Vollmer, & Amico, 2007; Mullis, Kay, & Williams, 2013; Sclafani, Rinaman, Vollmer, & Amico, 2007).

Palatable foods containing high levels of sugar, salt, and/or fat have become commonplace in western diets, and a corollary is the widespread overconsumption of food, leading to obesity-related diseases (World Health Organisation, 2015). Nearly two-thirds of the UK population is overweight or obese, and the proportion is increasing (UK Government, 2017). Excess body weight is an established contributor to a range of chronic health problems. For example, obese people are three times more likely to develop colon cancer than people with a BMI in

the healthy range; five times more likely to develop diabetes mellitus; and two-and-a-half times more likely to be hypertensive (UK Government, 2017). The prevalence of food-related cues compounds the difficulties experienced by people struggling to moderate their food intake: an attentional bias towards foods and food-related stimuli is apparent not only in overeaters, but also in the general population (Kumar, Higgs, Rutters, & Humphreys, 2016).

A limited but growing number of studies have examined the influence of oxytocin on weight management and eating, often with the aim of evaluating its potential as a treatment for overeating. In a small-scale study, Zhang et al. (2013) reported that 24 IU oxytocin administered to prediabetics 20 minutes before eating and at bedtime produced a decline in body mass over an eight-week period; moreover, postprandial glucose and insulin levels shifted towards healthier profiles. In the laboratory, Ott et al. (2013) found that oxytocin had no effect on the amount of breakfast eaten after an overnight fast but significantly reduced postprandial intake of chocolate biscuits in the same male cohort. Lawson et al. (2015) also measured food intake in fasted men, but found that oxytocin significantly reduced post-fasting breakfast consumption. Differences in menu choices and in the scheduling of food availability might account for oxytocin's disparate effects on food intake in fasted men across the two studies. Participants in the study by Lawson et al. (2015) were able to anticipate eating after ordering food from a menu, whereas Ott et al. (2013) provided a free-choice buffet from which participants could eat without delay. Sampling differences may also be relevant, as Lawson et al. (2015) tested a male cohort comprising both normal-weight and obese participants, whereas the Ott sample only included men with BMI scores in the healthy range. Recent findings from Thienel et al. (2016) indicated that oxytocin's effects on eating were stronger in an obese subgroup of an otherwise similar sample, suggesting that participant body mass may affect sensitivity to the effects of oxytocin.

Ott et al. (2013) and Thienel et al. (2016) also showed that biological markers of stress were significantly lower after oxytocin administration, a finding that is consistent with a number of other studies that have reported anxiolytic effects of oxytocin (Grimm et al., 2014; Mccullough, Churchland, & Mendez, 2013; Neumann, Torner, & Wigger, 1999). However, self-reported anxiety has not been measured previously in studies of oxytocin's effects on eating, so it is not yet known whether subjective changes in anxiety might be related to (and perhaps contribute towards) oxytocin's anorectic effect (Gibson, 2012; Wardle & Gibson, 2016). The present experiment, therefore, incorporated a self-report measure of anxiety.

Although neuropeptides have been found in human cerebrospinal fluid just 10 minutes after administration (Born et al., 2002), peak effects of oxytocin are theorised to occur between 30 and 90 minutes post intranasal administration, and this therapeutic window is usually adopted in human experiments (Gossen et al., 2012). However, the two previous studies of oxytocin's acute effects on postprandial snack-food intake employed a three-hour post administration interval, which makes their results difficult to compare directly with studies that have shown clinical effects of oxytocin 45 minutes after administration. For the first time in the context of oxytocin's effects on eating, the present study therefore employs a much shorter (but more typical) latency of 45 minutes between intranasal administration and the critical test.

The experimental aims were fully concealed to avoid undesirable demand characteristics and self-selection bias; participants were unaware that the study had anything to do with eating motivation, metabolism or energy expenditure. As a positive control, a partial replication of the study by Savaskan, Ehrhardt, Schulz, Walter, and Schächinger's (2008) was incorporated, testing oxytocin's effects on emotional face recognition. Because oxytocin has been shown to

reduce the post-prandial intake of sweet-tasting foods in rodents and in people, it was predicted that oxytocin would reduce the consumption of test foods given postprandially, particularly the sweet-tasting items, despite the much shorter latency between drug administration and testing.

2. MATERIALS AND METHODS

Design

A double-blind, placebo-controlled, randomised, and counterbalanced crossover protocol was implemented using a within-subjects design comprising two drug tests scheduled about a week apart. Participants were informed that the study investigated the effects of oxytocin on sensory perception across a range of modalities.

Participants

An opportunity sample of 20 healthy men aged 18 to 38 years (M = 23.5 yrs, SD = 6.5 yrs) with BMI scores ranging from 19.4 kg/m^2 to 30.8 kg/m^2 (M = 25.4 kg/m^2, SD = 3.1 kg/m^2) was recruited by word-of-mouth and/or in exchange for university course credits. Individuals with food allergies, diabetes, taking prescription medicines, pregnant, breastfeeding or on vegan diets were excluded. Altered endogenous oxytocin function is associated with high emotional arousal or stress (e.g. bereavement, financial windfall) so participants reporting such events were also excluded (Engelmann, Ebner, Landgraf, Holsboer, & Wotjak, 1999; Kovacs, 1986). Due to possible differences in taste sensitivity and suppressed eating (Audrain-McGovern & Benowitz, 2011; Gromysz-Kalkowska, Wojcik, Szubartowska, & Unkiewicz-Winiarczyk, 2002), regular smokers were also excluded. Participants were asked to avoid alcohol or non-steroidal anti-inflammatory drugs for 24 hours beforehand and to

abstain from consuming food and sugary drinks for two hours before the experiment, which was self-reported to the researcher (one participant was excluded). In order that participants were not in a fasted state when given access to the test foods, a meal of sandwiches and crisps/chips was consumed by all participants 25 minutes before access to the critical test foods, and participants provided ratings of their hunger before the snack test. If participants indicated that they were hungry on the VAS, did not eat lunch, or did not eat all of the lunch and had glucose levels below 4 mmol/L, they were excluded from further participation (no participants were excluded for these reasons). All participants gave written, informed consent to take part. The study was approved by the Research Ethics Committee at Kingston University.

Materials

A Salter's electronic food scale was used to weigh food and a needle-dial scale was used to weigh participants. Blood glucose levels were obtained using Accu-Chek's 'Aviv' hand-held monitor. Sham tasks used the following: Elite Healthcare's 'Two Point Discriminator Touch-Test'; synthetic almond- and soap-scented smelling bottles (Caravansons LLP, Bury, UK); and a stopwatch. Rubin's Romantic Love Scale (1970) and Higgs' (2015) VAS questionnaire measuring levels of alertness, stress, excitement, hunger, and thirst were completed together with a taste VAS measuring oatcake palatability, cracker saltiness, and chocolate biscuit sweetness. The pitch discrimination test from Music and Neuroimaging Laboratory was presented online (Schlaug, 2017). Bespoke materials for the sham visual tasks included A4-sized laminated colour prints of famous paintings and A6-sized laminated black-and-white pictures of castles for a 'spot-the-difference' test.

For lunch, each participant was provided with a meal of 546 kcal that was low in readily-

catabolizable sugars and consisted of a pre-packaged supermarket sandwich (Sainsbury's 'Cheese and tomato on malted bread', 424 kcal, 173 g) followed by a packet of plain crisps/potato chips (Hula Hoops, 121 kcal, 25 g). For the snack test, British equivalents of foods used in previous, similar experiments were sourced: chocolate cookies (Waitrose 'Triple Chunk Chocolate Chip', 127 kcal, 25 g per unit, 450 g per bowl), TUC Classic Crackers (17 kcal, 5.4 g per unit, 230 g per bowl), and Sainsbury's Oatcakes (47 kcal, 10.4 g per unit, 300 g per bowl). As per previous experiments, each snack-food type was matched for calorie content and macronutrients (see Table 1) and presented in a separate bowl filled to the top, in order that substantial amounts could be eaten without the bowl appearing empty.

	Chocolate Biscuits	Plain Oatcakes	Salty Crackers
Calories (kcal/100g)	501	488	518
Protein (g/100g)	5.7	10.7	6.9
Carbohydrate (g/100g)	59.5	56.9	54.2
Fat (g/100g)	25.8	23.5	29.9

Table 1. Nutritional values of the foods used for the taste test and the critical test of postprandial eating ("the snack test")

A positive control test was included to check that oxytocin was active (in case the effects on eating were non-significant) by attempting to replicate its actions on an unrelated psychological process: memory for faces (Savaskan, Ehrhardt, Schulz, Walter, & Schachinger, 2008). The facial recognition test (acquisition phase) employed a set of 60 colour pictures of Caucasian men (age range 20-65 years) with happy, angry, and neutral expressions on a white background. A further set of 50 colour pictures of Caucasian men (age

range 20-65 years) with neutral expressions and a white background was used for the recall test, 20 of which featured in the acquisition set but with angry or happy expressions, and 10 faces with neutral expressions were repeated from the acquisition set. Pictures were adapted from three databases: 'A lifespan database of adult facial stimuli' (Minear & Park, 2004), 'The NimStim set of facial expressions' (Tottenham et al., 2009) and the 'Stirling ESRC Face Database' (Psychological image collection, Stirling University.2017).

Oxytocin and placebo intranasal sprays were supplied by Victoria Pharmacy, Switzerland. The active ingredient of the oxytocin nasal spray was oxytocin together with excipients E 216, E 218 and chlorobutanol hemihydrate as preservatives. The placebo spray contained only excipients. A dose of 24 IU was administered, consistent with previous research (Ott et al., 2013).

Procedure

Participants were tested individually between 12:00 and 14:00 hrs. After providing informed consent and confirming compliance with the exclusion criteria, participants began the session with the face recognition task. They familiarised themselves with 60 face pictures (20 neutral, 20 happy, and 20 angry) presented in random order on a computer screen approximately 60 cm away for 10 seconds each with a 3 second break between stimuli. Immediately afterwards, participants self-administered either 24 IU of oxytocin or placebo under the supervision of the researcher with six puffs alternated by nostril every 30 seconds. Height and body mass were measured, and participants completed a measure of their romantic love status (Rubin, 1970), then 10 minutes later they were asked to eat the lunch provided. Because thirst can sometimes be experienced as hunger (Balleine, 1994), all participants were offered water with their lunch and indicated their thirst level on a VAS.

To support the purpose of the study as it had been described to the participants, a range of sham sensory tests was then presented. An online pitch test was conducted with the participant seated and responding via a computer keyboard to a series of diminishing pitch intervals presented through the computer's speakers (Schlaug, 2017). A two-point touch discrimination test on the right index finger was conducted to identify the smallest gap, in millimetres, that could be sensed. A smell test with smelling bottles containing synthetic soap or almond scents, depending on session, was then presented. Next was a timed balance test that required participants to stand on one leg while simultaneously 'drawing' counted numbers in the air, with their eyes shut, until they lost balance. At 30 minutes after oxytocin/placebo administration, a memory recognition test of the faces was undertaken. Just before the snack test, a finger-prick blood glucose test was conducted as a final check to ensure that participants did not have low blood glucose. Participants then completed a VAS measuring levels of 'happiness', 'excitement', 'alertness', 'anxiety', 'hunger', and 'thirst'. A few minutes before the covert snack test, a researcher provided the participants with small tasting samples of about a gram, one by one, from each of three tasting bowls containing 300 g of neutral snacks, 230g of salty crackers, and 450g of chocolate cookies. Participants rated each snack in turn on a 100 mm VAS line anchored with 'Not at all' and 'Very palatable' 'Very sweet' or 'Very salty' for the bland, salty, and sweet test foods, respectively. The final sham task involved presenting one of two near-identical spot-the-difference pictures for 30 seconds. Then the critical snack test occurred: at 45-minutes post-drug administration, the participant was instructed to enjoy a 10 minute 'cognitive break'; to let his mind 'relax'; and to select his preferred picture from a choice of five A4-sized prints of famous paintings. The experimenter announced that she would leave the room during the participant's 'cognitive break', and it was mentioned that the test foods would be thrown away after the experiment due to health and safety regulations, so the participants were free to help themselves to as

much of the foods as they wished. The snack test period lasted 10 mins, after which the second spot-the-difference picture was presented for 30 seconds, and the participant was asked to identify the differences between the two pictures. Before participants left, they were asked whether they thought they had been given oxytocin or placebo. The lunch foods and the snack test foods were weighed before and after testing, and the test sessions lasted about 75 mins in total. Figure 1 presents a visual timeline of the procedure.

Event sequence	**Time relative to drug administration**
1. Positive control task (memory test)	-15 mins
2. Oxytocin or Placebo given	0
3. Height and weight measured	
4. Time of last food recorded	
5. Romantic Love Scale	
6. Set lunch	+15 mins
7. Auditory pitch test	
8. Touch discrimination test	
9. Smell test	
10. Balance test	
11. Positive control task (memory test)	+30 mins
12. VAS self-report measures	
13. Blood glucose measure	
14. Taste test	+40 mins
15. Spot-the-difference picture 1	
16. SNACK TEST (‘cognitive break’)	+45 mins
17. Spot-the difference picture 2	+55 mins

Figure 1: Timeline of a test session

Statistical Analyses

Paired-samples t tests were conducted to test for differences in food intake and taste measures

between drug conditions. Due to multiple comparisons, a p-value of $p<0.005$ was taken as the threshold for statistical significance. Binary logistic regression was used to test for any effects of oxytocin on performance in the positive control (memory) task.

3. RESULTS

Food Intake

Table 2 presents mean scores for the eating measures and BMI. Intranasal oxytocin did not affect the amount of food consumed during the lunch ($t(19) = -1.06$, $p = .30$). However, intranasal oxytocin significantly reduced consumption of two of the test foods in the snack test. Specifically, the amount of chocolate biscuits eaten was significantly lower after oxytocin administration than after placebo administration ($t(19) = -3.51$, $p = .002$), and oxytocin also significantly reduced cracker consumption ($t(19) = -3.52$, $p = .002$). However, there was no significant difference between oxytocin and placebo conditions for the consumption of oatcakes ($t(19) = -1.44$, $p = .167$). Summing across food types, the total amount of test food consumed was significantly reduced by oxytocin ($t(19) = 4.15$, $p = .001$). Sweetness ratings for chocolate biscuits were higher in the oxytocin condition ($t(19) = 2.14$, $p = .046$), but not significantly so after adjustment for multiple comparisons ($p > .005$). The taste ratings for crackers and oatcakes were not significantly different between conditions (respectively: $t(19) = -.42$, $p = .68$; $t(19) = -1.79$, $p = .09$). As would be expected, BMI did not change between tests ($t(19) = 0.96$, $p = .35$).

	PLACEBO		OXYTOCIN	
MEASURE	Mean	SD	Mean	SD
Lunch eaten (g)	187.6	6.3	181.6	25.2
Chocolate biscuits eaten (g)	68.7	60.1	25.1	20.8
(kcal)	344.2	301.1	125.8	104.2
Crackers eaten (g)	19.4	18.0	5.7	6.8
(kcal)	100.5	93.2	29.5	35.2
Oatcakes eaten (g)	5.6	7.5	3.1	1.9
(kcal)	27.3	36.6	15.1	9.3
Total amount of test foods eaten (g)	93.7	67.4	33.9	23.3
Sweetness of chocolate cookies (VAS)	7.7	1.8	8.5	0.9
Saltiness of crackers (VAS)	5.8	1.8	5.7	1.9
Palatability of oatcakes (VAS)	3.5	2.3	2.5	1.9
BMI (kg/m^2)	25.5	3.1	25.4	3.0

Table 2: Means and standard deviations for food intake (expressed as g and kcal for test foods) and taste measures after the administration of oxytocin or placebo; also mean BMI scores (N=20 per condition, repeated measures).

Other Measures

No differences were found between oxytocin and placebo conditions on VAS measures of

anxiety, happiness, excitement, alertness, hunger or thirst, nor did blood glucose levels differ between drug conditions at the time of the snack test. For the positive control task (face recognition), logistic regression indicated that participants were more likely to respond correctly to a new face under the influence of oxytocin, compared with placebo, but only when oxytocin was administered in the second session; *Exp(B)* = .30, $p < .001$. Thus, the findings in our version of the memory test did not fully align with those of Savaskan et al. (2008).

4. DISCUSSION

In a double-blind, crossover, placebo-controlled experiment, 24 IU of oxytocin significantly reduced the consumption of chocolate biscuits and salty crackers by 20 healthy men, 45 minutes after drug administration. The reductions in consumption of both food types occurred postprandially, after having eaten a lunch, and in the absence of self-reported hunger. Anxiety and other aspects of mood were not affected by oxytocin. The results for food intake are strikingly consistent with those of Ott et al. (2013) and Thienel et al. (2016), which also found significant and pronounced effects of oxytocin on sweet-tasting carbohydrates specifically. In the present experiment, however, oxytocin reduced chocolate biscuit consumption to about one-third of placebo levels, whereas in Ott et al. (2013) the decline was was to about three-quarters of placebo levels. Sampling differences could account for this disparity, as the age range (25-27 years) and BMI range (22.3 to 23.2 kg/m^2) were much narrower in the study by Ott et al. (2013); in the subsequent study, the inclusion of obese participants may have contributed to an increased effect size (Thienel et al., 2016). Also, the chocolate biscuits were presented differently in our study, as whole (small) entities rather than as broken pieces. The results differ slightly from those of Lawson et al. (2015), who

only identified an effect of oxytocin when taking a combined macronutrient measure, with no selective effects on fat or carbohydrate subgroups, after controlling for multiplicity. Additionally, unlike any of the previous studies, the present experiment identified a significant reduction in salty snack consumption following oxytocin. Although this is the first report of oxytocin affecting intake of salty foods in humans, the finding is consistent with preclinical studies (e.g. Verbalis, Blackburn, Olson, & Stricker, 1993; Puryear, Rigatto, Amico, & Morris, 2001). The detection of an effect of oxytocin on salty food intake in the present study, in contrast with Ott et al. (2013), may reflect the shorter latency between drug administration and testing adopted here.

There was a tendency for chocolate biscuits to be rated as sweeter in the oxytocin condition than in the placebo condition. Typically, increased sweetness might be expected to correlate with increased palatability and (therefore) intake; however, oxytocin significantly reduced intake. Post hoc analyses indicated that the reduction in consumption of chocolate biscuits was not directly related to ratings of sweetness (Pearson's $r = 0.01$). Unfortunately, we did not test for the same taste parameters across all test foods, and so did not have ratings of general "palatability" for the chocolate biscuits to determine whether palatability was adversely affected by the elevated sense of sweetness. The absence of a general palatability measure makes it difficult to conclude that the intake of the more palatable test foods – chocolate biscuits and salty crackers - was specifically reduced by oxytocin regardless of whether the palatability was conferred by sweetness or saltiness. Ott et al. (2013) tested saltiness, sweetness, and palatability for each of the snack groups (bland, salty, and sweet), and only found the bland food to be rated more palatable after oxytocin. In contrast, we found no effect of oxytocin on oatcake palatability. However, the calories contained in the bland food used by Ott et al. (390 kcal/100g) were substantially lower than the calories found in the

salty and sweet foods (486 and 500 kcal/g respectively), meaning that the increased palatability rating in Ott et al.'s study could reflect a preference for low calorie foods in the oxytocin condition. In the present study, the test foods were also matched for calorie content (see Table 1). A need for more sophisticated characterization of taste properties in future studies is indicated in order to unpick the associations between sensation and behaviour. Currently, no study has reported associations between taste and intake that might logically underlie the effect of oxytocin.

Relatedly, we were also unable to identify a mediating role for anxiety-relief in explaining the effects of oxytocin on eating. Oxytocin administration is often associated with decreased anxiety (Mccullough et al., 2013) and in the studies by both Ott et al. (2013) and Thienel et al. (2016) biological markers of anxiety were significantly lower in the oxytocin condition. The inability to detect oxytocin-induced changes in self-reported anxiety in the current study may reflect the insensitivity of the VAS measure used, although changes in levels of HPA axis hormones may not necessarily be correlated with changes in subjective state. The present outcome accords with the findings of a review of the safety and side effects of oxytocin, which concluded that participants were unable to detect the presence of oxytocin either physically or through its behavioural effects (Mccullough et al., 2013). Participants in the present study were no better than chance at guessing on which session oxytocin was administered, and the effects occurred in the absence of any discernible changes in scores on Rubin's Romantic Love scale or on our other VAS mood scales. Together, these data suggest that individuals are unaware of measurable changes in their mood, behaviour or (more specifically) levels of anxiety brought about by oxytocin in a covert laboratory test.

It is noteworthy that previous studies have not always fully disguised their research aims,

introducing the possibility of undesirable demand characteristics. In the present study, we are confident that we concealed the purpose of the study, since nobody was able to articulate the real purpose of the experiment when questioned after completing the second test session. However, researcher effects may have been generated by (for example) the use of a female experimenter and an exclusively male, heterosexual cohort. It is not obvious how such effects may have operated to produce the drug-specific anorectic outcomes that we identified, but one possible route of influence is by affecting baseline eating propensity, which may in turn facilitate the detection of a drug effect. The instruction that the taste-test foods would be discarded if not eaten may have encouraged eating under oxytocin if the drug's prosocial actions included an increase in desire to avoid wastefulness in a social situation; however, the procedure is common to many studies that examine how particular variables affect food intake (including Ott et al., 2013). The role of the experimenter in modulating the effects of psychoactive drugs is a research issue that deserves further exploration (e.g. see Felisberti and Terry, 2015), particularly for a compound with prosocial effects, like oxytocin (Striepens, Kendrick, Maier, & Hurlemann, 2011).

Perhaps surprisingly, the pharmacokinetics of oxytocin are still not fully understood. A number of mechanisms have been proposed to explain how intranasal oxytocin might reach the brain (Dhuria, Hanson, & Frey, 2010), none of which have yet been ruled out (Madara, 2000). Neuropeptides have been detected in CSF just 10 minutes after intranasal application (Born et al., 2002), and intranasal oxytocin demonstrably enters CSF in primates (Lee, Scheidweiler, Diao, et al., 2018). Measurable effects from intranasal oxytocin have been reported in humans 30 minutes after administration (Savaskan, Ehrhardt, Schulz, Walter, & Schächinger, 2008). The contrasting latencies between drug administration and the first opportunity to eat, which were 15 minutes (to lunch) in this experiment and 45 minutes in Ott

et al.'s study (2013), made no difference: neither latency was associated with changes to appetite during this phase. However, the latencies between drug and snack-test also differed substantially between the two studies: 45 minutes here and 175 minutes in Ott et al. (2013); hence we demonstrated similar anorectic effects at a much shorter post-drug latency than reported previously. The speed of response in the current study would seem to rule out intracellular transmission as a mode of drug transport to the relevant receptors. More generally, the broad temporal range of oxytocin's efficacy at reducing food intake in the laboratory suggests that oxytocin's efficacy is not tightly reliant on time of administration. This could be important, given the potential difficulties for overeaters in maintaining a fixed eating regime (Zhang et al., 2013). However, a study in mice has shown the rapid development of tolerance to the anorectic effects of an oxytocin receptor agonist administered intranasally: the effects were negligible by day three of daily exposure (Olson et al., 1991). The possibility of tolerance in humans is yet to be explored, but a recent meta-analysis found that oxytocin becomes less effective at inhibiting eating with chronic administration (Leslie, Silva, Paloyelis, Blevins, & Treasure, 2018). Nevertheless, the potential for oxytocin to be an effective agent for dietary control with a practically-achievable dosage regimen supports the need for further research, particularly given the difficulties that many people would inevitably encounter in trying to maintain rigid schedules of drug administration and food consumption.

Intranasal oxytocin's effect on appetite has not yet been investigated in a normal-eating female cohort, which, given oxytocin's sexually dimorphic central expression (Ochedalski, Subburaju, Wynn, & Aguilera, 2007; Patisaul, Scordalakes, Young, & Rissman, 2003), is an important research area that still needs to be addressed. In female mice, oxytocin reduces appetite for sweet-tasting foodstuffs and curtails feeding in response to hyperosmotic and

lithium-induced toxicity (Flanagan, Verbalis, & Stricker, 1989; Verbalis,et al., 1993). However, oxytocin has a regulatory osmotic role unique to rodents that may make translational inferences unreliable (Blackburn, Samson, Fulton, Stricker, & Verbalis, 1995). More research with female participants is essential.

In conclusion, the current study identified significant anorectic effects of oxytocin on post-prandial food consumption, effects that are consistent with the limited number of studies that have been conducted to date. The consumption of a salty-food type as well as a sweet-food type was reduced by oxytocin, a novel finding consistent with animal data (Puryear, Rigatto, Amico, & Morris, 2001; Verbalis et al., 1993) The study has also demonstrated that such effects can be obtained within a much shorter timeframe after drug administration (45 minutes) than has been demonstrated in previous studies of oxytocin's anorectic effects.

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