Oxytocin and potential benefits for obesity treatment

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Purpose of review
Laboratory animal experiments have consistently shown that oxytocin causes early termination of food intake, thereby promoting a decrease in body weight in a long term. Recent studies have also assessed some of oxytocin’s effects on appetite and energy balance in humans. The present study examines the findings of the key basic research and of the few clinical studies published thus far in the context of potential benefits and challenges stemming from the use of oxytocin in obese patients.

Recent findings
Basic research indicates the involvement of oxytocin in satiety, processing, in reducing a drive to eat for pleasure and because of psychosocial factors. Although the results of clinical studies are very scarce, they suggest that oxytocin administered intranasally in humans decreases energy-induced and reward-induced eating, supports cognitive control of food choices, and improves glucose homeostasis, and its effectiveness may be BMI dependent.

Summary
Despite the wealth of basic research showing broad anorexigenic effects of oxytocin, clinical studies on oxytocin’s therapeutic potential in obesity, are still in their infancy. Future implementation of oxytocin-based pharmacological strategies in controlling energy balance will likely depend on our ability to integrate diverse behavioral and metabolic effects of oxytocin in obesity treatment regimens.

Keywords
feeding, hunger, oxytocin, satiety, sugar

INTRODUCTION
As excessive energy intake appears to be the main contributory to the obesity ‘epidemic’, the search for pharmacological strategies to address this health issue has been focused on identifying molecules that promote early satiation and decrease a drive to eat for reward. In the past several years there has been an enhanced interest in the anorexigenic properties of oxytocin, a 9-amino acid G protein-coupled receptor (OTR) endogenous ligand, synthesized primarily by neurons in the hypothalamic supraoptic (SON), and paraventricular (PVN) nuclei that project to numerous central regions and to the neurohypophysis [1–3]. This interest in potential applications of oxytocin ligands in obesity treatment arose upon the analysis of animal research data showing the ability of oxytocin to induce early termination of food intake and diminish feeding reward.

OXYTOCIN AS AN ANOREXIGEN: KEY LABORATORY ANIMAL RESEARCH FINDINGS
Ample evidence links oxytocin signaling with the regulation of meal size and – in the long term – body weight. The ablation of the PVN and the disruption in connectivity between the PVN and the brain stem lead to voracious feeding and obesity in rats [4–6]. Deficiencies in the PVN oxytocin synthesis (e.g. in the Sim-1 mutation murine model) underlie excessive calorie intake and overweight, and exogenous oxytocin corrects the resulting energy imbalance [7]. Termination of eating is associated with elevated activity of PVN oxytocin neurons and neurohypophyseal release of the hormone (6, 18–20). It has been shown that oxytocin is a part of essential neural and endocrine pathways (including the gut–brain axis) that regulate meal size. Hence, oxytocin has been found to be functionally intertwined with satiety

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Curr Opin Endocrinol Diabetes Obes 2017, 24:000–000
DOI:10.1097/MED.0000000000000351
Obesity and nutrition

KEY POINTS

- In animals, central and peripheral administration of oxytocin reduces appetite and, in a longer-term, body weight.
- The central pool of the oxytocin receptor affects a broader range of appetite-related behaviors, including those associated with reward.
- Intranasal oxytocin in humans reduces energy-driven and reward-driven consumption, and its effectiveness seems BMI dependent.
- Psychosocial, cognitive and metabolic effects of oxytocin should be incorporated in conceptualizing its use in obesity treatment.

Oxytocin signaling has been linked with physiological parameters stemming from consumption, including stomach distension and salt loading [13,14]. Furthermore, oxytocin promotes a termination of intake of toxic tastants by engaging a dispersed hypothalamic, hindbrain, and amygdala circuit [15]. The amount of food ingested after energy deprivation can be reduced by administration of oxytocin into the cerebral ventricles [16,17] and specific brain areas, such as the brain stem, ventromedial hypothalamic nucleus (VMH), nucleus accumbens (Acb), and ventral tegmental area (VTA) [18,19,20,21]. Despite very limited ability to cross the blood–brain barrier (BBB), peripherally injected oxytocin reliably decreases intake of energy-dense chow [16,22]. The anorexigenic and adiposity-reducing effects of oxytocin are sustained in longer-term treatment regimens [12,17,23].

Because oxytocin terminals are localized in proximity to reward-related neuregulators such as dopamine and opioids [24,25,26], some had hypothesized that oxytocin might affect reward-motivated behaviors. Indeed, activation of the OTR in the Acb core decreases methamphetamine-seeking behavior [27] and attenuates methamphetamine-induced and alcohol-induced conditioned place preference (CPP) in rats [28,29]. Food intake studies suggest that centrally acting oxytocin decreases palatability-driven and macronutrient-driven aspects of consumption, including opioid-induced hyperphagia [30]. In particular, appetite for carbohydrates, and for saccharin, seems to be affected. Injections of oxytocin into the VTA and Acb are especially effective in reducing intake of sweet solutions [19,20]. Mice injected intraperitoneally (IP) with a BBB-penetrant OTR antagonist, L-368,899, elevate consumption of carbohydrate and saccharin solutions, but not lipid emulsions [31,32]. This outcome parallels increased preference for carbohydrates and saccharin in oxytocin knockout mice [33]. One should note that the effect of oxytocin on macronutrient preference may be modified by energy density of food (hence, by the energy-driven component of feeding). For example, oxytocin injections reduce intake of sucrose-free yet palatable high-fat chow and genetic deletion of oxytocin neurons promotes obesity in rats fed energy-dense high-fat food [17,34].

HUMAN STUDIES

Endogenous oxytocin and relationship with appetite and body weight dysregulation

The few studies published to date point to a relationship between the functioning of the oxytocin system and obesity in humans. Qian et al. reported that blood oxytocin levels were significantly lower in obese versus normal-weight individuals, and several obesity-related parameters (BMI, waist circumference, waist-to-hip ratio, cholesterol, and homeostasis model assessment of insulin resistance) were negatively correlated with oxytocin plasma concentrations, [35]. In women, obesity underlies the need to administer higher doses of IV OT to induce labor [36,37,38]. Limited genetic information suggests that changes in the OTR gene contribute to appetite and body weight dysregulation, although the outcome tends to be associated with other psychological and psycho-social factors. This is not surprising considering the antianxiety and pro-social roles of oxytocin [39]. For example, Bush et al. found that children carrying 1 (AG) or 2 (AA) copies of an OTR SNP (rs53576) associated with lower affinity binding of oxytocin, display greater BMI and adiposity when raised in a low socioeconomic status (SES) [40]. The GG genotype of this SNP is associated with binge eating [31]. This study also found that A allele carriers of another OTR SNP, rs2254298, who had received poor maternal care, had four-fold higher odds of bingeing.

Oxytocin treatment and appetite

The initial results of the effect of exogenous oxytocin in humans on appetite-related parameters did not parallel animal data. Borg et al. gave healthy volunteers a liquid diet (13% protein, 48% carbohydrate, and 39% lipids) and oxytocin was infused intravenously at 20, 40, or 80 mU/min throughout
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...the meal [41]. Surprisingly, the oxytocin-treated patients consumed the same volume of the diet and their gastric emptying rate was unaffected. The poor BBB permeability of oxytocin was speculated as a cause of the ineffectiveness of the treatment, but it might not have been the sole reason. The recent rodent studies suggest that consumption of liquids whose energy density is typically lower than in solid food, is not as sensitive to pharmacological modification by peripherally administered OTR ligands regardless of their ability to cross the BBB. For example, IV OT in rats does not affect the intake of palatable solutions even in energy-deprived animals, but it is effective in reducing postdeprivation intake of chow [22]. The BBB-penetrant OTR antagonist, L-368,899, injected IP in mice having access to sugar and fat solutions, shifts only taster preference, without affecting the overall consumption [42]. In nonchoice scenarios, L-368,899 increases only consumption of sweetened liquids [42,43]. Hence, peripheral injections of OTR ligands might be potentially useful in modifying dietary preferences, but not in controlling energy intake from calorie-dilute liquids.

Because oxytocin does not readily cross the BBB and the effects of systemic injections are thus mediated by brain sites where the barrier is weak, the focus shifted to intranasal oxytocin delivery. This route is superior in engaging a broader set of central mechanisms: it increases peptide plasma levels and, importantly, peptides can cross the olfactory epithelia, be transported within cerebral perivascular spaces and/or enter the brain along the cranial nerves [44–46]. Our understanding of the time course for intranasal oxytocin to reach peripheral and central targets remains elusive, especially considering that the reported discrepancy in maximum plasma levels is 10–90 min posttreatment and the oxytocin tmax for the cerebrospinal fluid is 75 min, not to mention that those values pertain mostly to males [47–50]. Nonetheless, the data from animal models (from rodents to macaques) support the notion that the intranasal oxytocin delivery produces feeding changes consistent with the roles of CNS targets that regulate specific facets of consumption [51–55]. Accordingly, the few studies investigating potential anorexigenic effects of intranasal oxytocin in humans thus far have produced exciting results pertaining to eating for both energy and reward; although, because of the scarcity of the data, less intuitive outcomes are open to interpretation.

Ott et al. [56] gave overnight food-deprived adult males 30-min access to a breakfast buffet followed 1 h 40 min later by a snack choice of sweet chocolate chip cookies, rice waffles, and salty crackers. Forty-five minutes before the breakfast (but not before the snack), the participants received 24 IU oxytocin intranasally. Although food intake or hunger ratings were unaffected at breakfast, oxytocin decreased snack consumption. In line with the proposed role of oxytocin in reducing reward-driven intake of sweet foods [39], the diminished consumption of cookies was the sole contributor to the overall decrease in snacking. However, the lack of effectiveness of oxytocin on hunger-induced breakfast intake was surprising. Subsequently, Lawson et al. [57] utilized a different study design and provided evidence that oxytocin can reduce consumption for energy in humans. Patients were also given breakfast; however, they received two predetermined menu items 60 min after the oxytocin treatment, and they were allowed to eat for 1 h [57]. Intranasal oxytocin diminished energy consumption and decreased fat intake, whereas oxytocin-induced reduction in ingestion of protein and carbohydrates showed a trend but did not reach significance. Thus, when intake of high-calorie food is motivated by energy needs, then – in agreement with the results of animal studies [17], fat intake is effectively reduced by oxytocin. Elevated CCK levels might have possibly contributed to facilitating early satiation, although this can be speculated based only on earlier basic research [17,58,59]. The outcomes of the Lawson et al. versus Ott et al. studies appear to exemplify a profound importance of macronutrient composition and food choices available in a meal, energy density of food, and of energy status of a patient, in inducing specific anorexigenic effects of intranasal oxytocin.

Adding to the complexity, Thienel et al. [60] employed the same protocol as Ott et al. [56] and found that oxytocin administered intranasally 45 min before breakfast buffet in obese men was effective in decreasing energy intake (and carbohydrate intake) in consumption stimulated by hunger (breakfast) and by reward (snack). Taken together, these studies suggest that both a temporary energy state and excessive energy stores affect individual responsiveness to anorexigenic properties of intranasal oxytocin [60]. In fact, in the 2013 pilot clinical study, Zhang et al. showed particular sensitivity of high-BMI patients to chronic intranasal oxytocin in reducing body weight [61]. The authors treated obese individuals (mixed male and female cohort) with oxytocin four times per day (20 min before each of the 3 daily meals and before sleep) for 8 weeks and noted a decrease in body weight by 8.9 ± 5.4 kg. Interestingly, the magnitude of weight loss was more pronounced in patients with higher BMIs, thereby corroborating acute oxytocin treatment findings [60]. From a therapeutic point of view, it is promising that obese subjects
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might respond particularly well to intranasal oxytoxin both in consumption driven by energy and by reward, although this notion should be still approached with caution, as BMI was not a modifying factor in the Lawson et al. [57] meal paradigm.

One should note that pleasure of consumption is not solely dependent on the gustatory attractiveness of a tastant. In the obesogenic environment, cognitive processes play a crucial role in making food choices. The known consequences (benefits/rewards) of consumption (short term: pleasant taste; long term: metabolic health) shape food intake [62,63]. Striepens et al. [64**] have recently reported that normal-weight females treated with oxytocin display reduced food craving when asked to reflect on the long-term effect of frequent intake of desserts. When asked to think of the immediate consequences of consuming palatable food, individuals showing a restrictive eating style experienced reduced craving after intranasal oxytocin. This effect on cognitive control of consumption was paralleled by activity changes in relevant brain sites, including the prefrontal cortex [64**], which has been implicated in processing long-term and short-term rewards [65,66]. It obviously remains to be elucidated whether oxytocin treatment could have a positive impact on food craving in obese individuals. However, considering that transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods [67], the ability of oxytocin to modify eating might also extend onto influencing dietary choices through cognitive/motivational processing in obese subjects.

**ENVISIONING THE WAY FORWARD: BETWEEN BENEFITS, CONCERNS, AND GAPS IN KNOWLEDGE**

The results of the few human studies performed thus far indicate that continuation of studies on anorexigenic and, consequently, antiobesity effects of oxytocin, is warranted. From the standpoint of appetite regulation, the potential benefits of oxytocin treatment include inducing early satiation in energy-driven consumption and diminishing the short-term and long-term rewarding value of ingesting palatable tasters. Based solely on the data obtained in animals [17*,18,34,68], but not yet confirmed in humans, aside from reducing appetite, oxytocin might additionally aid in body weight loss by increasing energy expenditure. There is a particular need to address the issue of timing of drug administration, developing ligands that can better target specific (especially, central) subpopulations of the OTR (thereby, simultaneously reducing the likelihood of affecting the vasopressin receptor, which is one of the critical current concerns), and dietary strategies that could enhance responsiveness to the treatment in patients that differ in the nature of metabolic pathophysiology.

Considering whether to continue studies on oxytocin-based therapies in obese patients, one should also take into account the potentially beneficial effect on glucose homeostasis that can be achieved independently from body weight outcomes; this may be critical in the care of obese individuals as type 2 diabetes is a typical comorbidity. Already in the 1980s, Chiodera et al. [69] reported that in subjects treated with 6 mU oxytocin intravenously, insulin levels were significantly higher after intravenous glucose infusion. Most recently, intranasal oxytocin has been found to attenuate the peak excursion of blood glucose and to augment the early elevation in insulin levels in the oral glucose tolerance test [70]. In the Lawson et al. [57] study, intranasal oxytocin lowered HOMA insulin resistance index and fasting insulin levels. Ott et al. [56] found that intranasal oxytocin curbed the meal-related rise in the blood glucose concentration.

One of the greatest challenges in the therapeutic use of oxytocin is this molecule’s involvement in numerous processes, including parturition, lactation, sexual behavior, sociality and emotional processing [71]. Yet this difficulty can in fact present an opportunity in that it can help identify specific pathologies and physiological states conducive to developing excessive body weight in which oxytocin could be a particularly effective anorexigen while – simultaneously – improving other symptoms. To exemplify this approach, clinical studies on the Prader–Willi syndrome (PWS) have already shown benefits of such multifaceted pharmacological strategy. Loss-of-function changes in the oxytocin circuit, including a decrease in the number and size of hypothalamic oxytocin neurons and a dysregulation of oxytocin release, underlie this PWS; key symptoms include abnormal social behavior, excessive food intake, and food cravings [32,72*]. The intranasal oxytocin regimen has been found to improve both social and food-related behaviors in PWS children [73**,74*,75].

**CONCLUSION**

The few clinical studies performed to date suggest that pharmacologic targeting of the OTR might have beneficial effect on inducing early satiation, reducing the drive to eat for reward and improving glucose homeostasis. It appears that the likelihood of successful implementation of oxytocin-based pharmacological strategies in alleviating excessive
appetite and body weight will depend on our ability to utilize oxytocin as a common molecule in an integrated behavioral and metabolic approach to treating obesity.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the Royal Society of New Zealand Marsden grant.

Conflicts of interest

There are no conflicts of interests

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the period of review, have been highlighted as.

of special interest

of outstanding interest


The data suggest that not only is central oxytocin effective in reducing food intake and body weight over the course of a chronic treatment, but it also promotes a decrease in body weight for several days after discontinuation of the drug regimen.


The findings from animal models indicate that oxytocin acting directly at a key reward site, the nucleus accumbens, decreases food intake driven by energy and palatability.


The very first paper showing that, unlike centrally acting oxytocin, peripheral administration of this peptide does not affect the intake of calorie-dilute solutions, while retaining its effectiveness in reducing consumption of energy-dense foods.


Basic research findings that provide a neuroanatomical basis of the functional relationship between oxytocin and reward systems.


This paper identifies the ability of oxytocin at subthreshold anorexigenic doses to interfere with opioid-driven increase in appetite.


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Socioeconomic disparities in childhood

Borg J, Simren M, Ohlsson B. Oxytocin reduces satiety scores without increased brain and plasma.


This is an important study that further substantiates the basic research findings that oxytocin is particularly effective as an anorexigen in individuals with a high BMI.


13. An important study showing aberrant oxytocin release in patients suffering from the PWS, which is associated with extreme hyperphagia.


15. The authors present clinical evidence showing effectiveness of oxytocin in treating combined eating and social behavioral PWS symptoms, capitalizing on the pleiotropic effects of this neurohormone.


This report shows that intranasal oxytocin at a relatively low dose (16IU) is a safe, well tolerated treatment that improves some hyperphagia-associated PWS parameters.