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# Oxytocin as a Potential Pharmacological Tool to Combat Obesity

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## Abstract

The neuropeptide oxytocin (OT) has emerged as an important anorexigen in the regulation of food intake and energy balance. It has been shown that the release of OT and activation of hypothalamic OT neurons coincide with food ingestion. Its effects on feeding have largely been attributed to limiting meal size through interactions in key regulatory brain regions governing the homeostatic control of food intake such as the hypothalamus and hindbrain in addition to key feeding reward areas as the nucleus accumbens and ventral tegmental area. Furthermore, the magnitude of an anorexigenic response to OT and feeding-related activation of the brain OT circuit are modified by the composition and flavor of a diet as well as by a social context in which a meal is consumed. OT is particularly effective in reducing consumption of carbohydrates and sweet tastants. Pharmacologic, genetic, and pair-feeding studies indicate that OT-elicited weight loss cannot be fully explained by reductions of food intake and that OT's overall impact on

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Conflicts of Interest

JEB no longer has a financial interest in OXT Therapeutics, Inc., a company that had developed highly specific and stable analogs of oxytocin to treat obesity and metabolic disease. The authors' interests were reviewed and are managed by their local institutions in accordance with their conflict of interest policies. The other authors have nothing to report.

energy balance is also, due in part, to OT-elicited changes in lipolysis, energy expenditure, and glucose regulation. Peripheral administration of OT mimics many of its effects when it is given into the CNS, raising the questions of whether and to what extent circulating OT acts through peripheral OT receptors to regulate energy balance. While OT has been found to elicit weight loss in female mice, recent studies have indicated that sex and estrous cycle may impact oxytocinergic modulation of food intake. Despite the overall promising basic research data, attempts to use OT in the clinical setting to combat obesity and overeating have generated somewhat mixed results. The focus of this mini-review is to briefly summarize the role of OT in feeding and metabolism, address gaps and inconsistencies in our knowledge and discuss some of the limitations to the potential use of chronic OT that should help guide future research on OT as a tailor-made anti-obesity therapeutic.

### Keywords

Obesity; oxytocin; food intake; meal size; energy expenditure

## Introduction

Over three decades have passed since the reports by Arletti and colleagues showing the ability of exogenously administered neurohormone oxytocin (OT) to reduce feeding behavior in the laboratory rat [1, 2]. These findings extended earlier work by Verbalis and colleagues who found that ingestion of food also increased OT secretion which led them to propose that OT release is involved with inhibiting ingestion of food [3]. Since that initial discovery, a wealth of evidence has been generated not only supporting the link between OT and meal cessation, but also expanding our understanding of the role of OT in energy balance and ingestive behavior control onto reward, gut-brain signaling, protection of internal milieu and metabolic processing. The results of the many years of research have been promising enough to lead to clinical trials aimed at reducing body weight in humans.

In the first part of this minireview, we provide a brief overview of the key findings pertaining to the role of OT in feeding and metabolism. The second part, focusing on gaps and inconsistencies in our knowledge and defining limitations associated with the use of OT in pharmacotherapy of obesity, has been devised to help guide future research endeavors toward optimizing treatments that utilize OT.

## 1. Oxytocin, feeding and metabolism: overview of key findings

### 1.1. Oxytocin and early meal cessation

The notion that brain pathways encompassing OT might be involved in the regulation of meal size could be inferred from early studies focusing on the disruption of the hypothalamic circuit involved in energy homeostasis. The ablation of the paraventricular nuclei (PVN) of the hypothalamus – where OT is synthesized - as well as the severing of the pathways between the brain stem and the PVN in laboratory animals led to overfeeding [4-7].

Since these initial discoveries substantial evidence has linked OT with termination of food intake. Male and ovariectomized female rats show either a progressive increase in plasma OT that occurs throughout the course of a meal or at 2-hours following meal initiation (likely at the end of a meal when the cessation of feeding is driven by satiation) [3, 8]. While activation of neurohypophyseal OT release can be stimulated by stomach distension and elevated plasma osmolality, which are the phenomena that accompany ingestion of large (i.e., satiating) amounts of food [9-11]), the data are not always consistent as high sugar intake can also activate SON OT neurons in the absence of changes in plasma osmolality [12]. Mice and rats allowed to eat until reaching satiation display a higher number of neurons expressing c-Fos in the PVN and supraoptic nuclei (SON) of the hypothalamus than at the beginning of a meal. Though the meal-end percentage of activated OT neurons differs depending on the macronutrient composition of food as well as its caloric density, it nonetheless is significantly higher in comparison to the control fasted condition regardless of the parameters of a diet [13-15]. In addition, decreased OT signaling [e.g. by application of an OT-receptor antagonist into the fourth ventricle; or global genetic knock-out of OT receptors or reduction of OT receptors within the nucleus tractus solitarius (NTS)] is associated with increased food intake/meal size [15-18]. Finally, OT mRNA within the hypothalamus or PVN is either increased in response to sugar relative to fat [14] or feeding status, as fed animals have elevated OT mRNA relative to fasted animals and this is restored by either refeeding [19] or leptin administration [20, 21]. In addition, in select brain areas, OT receptor expression is decreased in fed animals relative to fasted animals [22, 23].

It should be emphasized that the OT system is affected by the vast majority of treatments that promote early termination of feeding, including administration of peptides and neuropeptides involved in feeding control. For example, leptin [20, 24-27], cocaine-amphetamine related transcript (CART) [28], alpha-melanocyte stimulating hormone (alpha-MSH) [29], adrenomedullin family [30], and glucagon-like peptide-1 [31-34] administered at anorexigenic doses activate OT neurons. Conversely, delayed satiation induced through injection of hyperphagic opioid receptor agonists or Agouti-related protein, is associated with a decrease in OT neuronal activation [35, 36]. While this mini-review does not provide an in-depth description of the complex integration of OT and other anorexigenic peptides, the upstream regulators and downstream targets of OT in the control of food intake has been reviewed elsewhere (for review see [37, 38])

While the link between endogenous OT and termination of feeding is important from the physiological point of view, a plethora of pharmacological studies have shown a remarkable effectiveness of exogenous OT as an appetite suppressant. Already in the first reports identifying OT's action on feeding, intracerebroventricular (ICV) and intraperitoneal (IP) OT were found to produce a short-lived hypophagia in rats [1, 2]. OT was effective in reducing chow intake in rats maintained under a 3-hour daily meal regimen by increasing latency to begin a meal and decreasing meal duration. Subsequently, lateral or third ventricular OT was shown to decrease meal size in ad libitum fed rats [39] and in rats stimulated to eat by deprivation and to reduce the time spent eating in animals accustomed to having a 1-hour meal [40]. Apart from ICV and IP routes, the ability of OT to promote early termination of feeding has been since established for subcutaneous (SC), intravenous (IV), intranasal (IN), third ventricular (3V) and fourth ventricular (4v) routes

(for review, see e.g.[38]). Importantly, direct infusions of OT into brain areas responsible for various aspects of eating, from the pleasure of consumption to energy needs, including the ventromedial hypothalamic nucleus (VMH), nucleus accumbens (NAcc), amygdala, and ventral tegmental area (VTA), reduced the amount of solid and liquid diets consumed during a meal. Additionally, chemogenetic and optogenetic manipulation of glutamatergic neurons in the arcuate nucleus that express the OT receptor, induced rapid satiety [41].

While OT reduces meal size, substantial evidence suggests that this stems largely from accelerating satiation rather than reducing the perception of hunger. As demonstrated in recent operant studies in rats, unlike drugs that shift animals' ability to discriminate the hungry state, peripheral OT does not affect the feeling of hunger. Instead, it is effective in generating early cessation of a meal that has already started [42].

### 1.2. Oxytocin and reward-based eating

While it is well established that OT acts acutely to regulate food intake via enhanced satiation, emerging evidence suggests that OT induced satiation may be achieved, in part, by reducing rewarding aspects of the ingested foods. OT neurons send projections to many regions implicated in brain reward circuitry, including areas of the mesolimbic reward pathway [43-47]. Moreover, evidence from rodent studies suggests that OT acts directly within the mesolimbic pathway to inhibit food intake [48-50]. For example, OT acts in the NAcc core to reduce intake of sucrose and saccharin solutions in non-deprived animals without promoting malaise [49]. Similarly, OT administration to the VTA reduces sucrose intake, whereas OT receptor antagonist increases sucrose intake in rats [50]. In overweight or obese human males, intranasal OT reduces blood oxygen level-dependent responses in the VTA, orbitofrontal cortex, insula, globus pallidus, putamen, hippocampus, and amygdala in response to high calorie vs non-calorie food items, and increased responses in the anterior cingulate and frontopolar cortex, suggesting a reduction in reward and motivational regions with enhanced activity in cognitive control [51]. Functional connectivity analyses further show that OT reduces functional connectivity between the VTA and areas involved in food motivation, such as the insula, oral somatosensory cortex, amygdala, hippocampus, operculum, and middle temporal gyrus in response to the images of high-calorie vs non-calorie food [52]. Thus, taken together, OT acts through brain regions associated with reward and motivation to decrease food intake in rodents and intranasal OT modulates activity in analogous brain regions in response to food cues in humans.

In support of the idea that OT acts via modulation for rewarding aspects of eating, it is important to note that OT has a pronounced effect on modulating intake of palatable and or/sweet foods [49, 53-55]. Early evidence of this utilizing rodent models showed that ICV OT administration reduces sucrose intake in food deprived rats by 45%, [56]. Additionally, OT knockout (KO) mice demonstrate enhanced intake of both nutritive and non-nutritive carbohydrate and sweet tasting solutions, however, not all palatable foods are modulated by OT as there was no effect of OT KO on intake of palatable fat emulsions [57, 58]. These findings extend to humans as well. For example, in men, intranasal OT preferentially reduces intake of palatable foods [59-61]. Indeed, administration of intranasal OT in men reduced the intake of a post-meal "snack" of chocolate cookies by 25% but had no effect

on hunger driven food intake at a breakfast buffet [61]. While the timing of the snack intake was much later than the buffet relative to OT administration (3 hours vs 45 min), presenting a notable confound, Burmester et al., found that OT reduced palatable snack intake at 45 min post administration in men [62]. Moreover, OT reduces intake of both sweet chocolate cookies and salty crackers, without affecting intake of the lunch meal or the food that was rated the least palatable of the three snack options (oatcakes), together suggesting that palatability might be the critical factor in OT mediated anorexigenic effects. In a similar test in females, however, OT reduced post-prandial intake of chocolate cookies, but had no effect on intake of oat cakes or salty crackers [63]. This raises some question as to whether there may be some sex differences in the intensity or specificity of OT-induced reward-based eating, an area that requires further investigation.

In addition to reducing intake, OT has been shown to impact food motivated behaviors. Oxytocin delivered to the lateral ventricle, NTS or VTA reduces motivation to work for palatable sucrose pellets in a progressive ratio operant responding task [48], and motivation to work for sucrose in a free chow vs operant sucrose choice task [64]. The impact of OT on food motivated behaviors are likely mediated, in part, via action in the mesolimbic dopamine pathway. Indeed, lateral ICV OT reduces food cue induced dopamine neuron activity in response to Pavlovian cues associated with sucrose access in the VTA [64]. Similar to food motivated responding, lateral ventricular OT administration reduces impulsive operant responding for palatable food [64]. Impulsive behavior is mediated both by perceived value of the reward and inhibitory control, and therefore OT modulate one or both of these aspects of impulsivity. Given that OT reduces motivated responding for sucrose, it is possible that this aspect of OT alone is sufficient to account for reduced food impulsive behavior. However, evidence from human studies suggests that OT activates brain regions involved in inhibitory control, such as the ventromedial and ventrolateral prefrontal cortex, anterior cingulate cortex, and supplemental motor area, in response to high vs low calorie food cues [65]. Further research is warranted in order to determine the extent to which OT modulates inhibitory control of eating behavior. As each of the rodent studies related to food motivated behavior and impulsivity described above could be confounded by the general effects of OT on sucrose satiation signaling, it is important to note that lateral ventricular OT also reduced conditioned place preference for a high fat/high sugar food in the absence of food consumption, indicating that OT does indeed reduce palatable food-seeking behavior once animals are conditioned to associate the food with a context [64].

### 1.3. Activation of oxytocin systems by acute gastrointestinal signals

In the last decades, several pieces of evidence have shown that different gastrointestinal peptides released after meal consumption affect the activity of magnocellular and parvocellular OT neurons by mechanisms involving direct or indirect pathways. In turn, the activation of OT systems leads to both central and peripheral OT release, which affects energy homeostasis and feeding behavior [55, 66].

Early studies showed that intravenous (IV) administration of the satiation signal cholecystokinin (CCK) cause an increase in Fos expression of SON and PVN OT magnocellular neurons and some PVN parvocellular neurons in rats [67]. This effect is

accompanied by a transient (~10 min) enhancement of the electrical activity, a rapid rise in OT content in plasma, and somatodendritic OT release [3, 11, 68-70]. Moreover, the magnitude of the OT peripheral release in response to CCK has been shown to be affected by the feeding state when CCK is given [5], indicating that other factors also modulate this response. Subsequent studies have shown that this OT activation is mediated indirectly by vagal inputs, which activate NTS A2 noradrenergic cells that project fibers to the SON to elicit excitatory effects on OT neurons [71].

Similarly, systemic administration of the gut-derived hormone secretin, which has also been implicated in satiation signaling, causes a robust increase of the electrical activity in OT neurons in rats. The effects of secretin on OT cells are of greater magnitude than the ones induced by IV CCK and last ~20 – 30 min, the rise in plasma content shows a dose-dependent fashion. Like CCK, this response is mediated by excitatory afferent noradrenergic pathways [72]. In addition to an indirect mechanism, secretin may also act directly on OT neurons: intracerebroventricular (ICV) administration triggers Fos expression in SON, but not PVN, OT neurons that is also accompanied with a rise in OT content in plasma, this effect is believed to be mediated by secretin receptors expressed by SON cells, as secretin receptor-null mice fail to elicit Fos activation [73]. Since secretin penetrates the blood-brain barrier [74], the evidence suggests that, after being released from duodenum S cells, secretin may exert different modes of action on OT systems to exert, possibly, fast- and long-term effects.

In addition to the OT release stimulated by gut-released peptides, recent evidence indicates that OT systems also play a role related to carbohydrate metabolism and glucose homeostasis, leading to the notion that OT can be a relevant player involved in nutrient selection. In line with this, both gavage feeding and intake of a high-sugar foods have been shown to increase the activity of OT neurons in rats [12] and enhance the expression of OT mRNA transcripts in mice [75]. In hypothalamic explants containing the SON, glucose itself and glucose plus insulin have been shown to increase intracellular calcium concentration $[Ca^{2+}]_i$ and elicit OT release, respectively; these responses were dependent on glucokinase activity [76], suggesting that OT neurons may be intrinsically glucose-sensitive cells. On the other hand, it has been recently shown that IV administration of insulin results in a progressive and long-lasting (+1h) activation of OT SON magnocellular neurons, and this response cannot be reversed by restoration of blood glucose to initial concentrations [77]. This activation pattern following insulin IV is remarkably similar to the observed response to sweet-condensed milk, but not isocaloric fat, gavage [12]. Furthermore, both responses can be abolished by ICV administration of the insulin receptor antagonist S961 [77]. This pattern of OT activation is consistent with previous studies reporting gradual intake of insulin into the CSF by a saturable transport mechanism at the blood brain barrier (BBB) [78-80]. Finally, direct (ICV) insulin administration results in increased $[Ca^{2+}]_i$ in PVN OT cells and peripheral OT release [81].

### 1.4. Activation of central oxytocin system by pathophysiological conditions

A unique genetic rat model that expresses the OT-monomeric red fluorescent protein 1 (mRFP1) fusion gene in the SON and PVN was generated to identify OT neurons

under fluorescent microscopy without immunohistochemistry [82]. In this transgenic rat, magnocellular OT neurons located in the SON and PVN express mRFP1 fluorescence, and nerve terminals projected from the magnocellular OT neurons into the posterior pituitary (PP) exhibit intense mRFP1 fluorescence in the PP. It is known that the parvocellular PVN OT neurons project axon terminals to brainstem regions such as the NTS, the dorsal motor nucleus of the vagal nerve (DMV), and the spinal cord. In this transgenic rat, OT-mRFP1 nerve terminals in the brainstem and the spinal cord are visualized as mRFP1 fluorescent granules under fluorescent microscopy [83-85].

The intensity of mRFP1 fluorescence in the SON and PVN and number of mRFP1 granules in the nerve terminals projected from parvocellular OT neurons in the brainstem and spinal cord tend to depend on OT synthesis and accumulation. It is well demonstrated that peripheral administration of CCK-8 and secretin activates central OT neurons and stimulates secretion of OT in rats [72, 86]. In OT-mRFP1 transgenic rats peripheral administration of CCK-8 and secretin caused induction of Fos-ir in OT-mRFP1 neurons in the SON and PVN and caused a significant increase of mRFP1 fluorescence intensity in the OT-mRFP1 neurons in the SON and PVN and number of mRFP1-positive granules in the NTS [84, 87]. These results suggest that peripheral administration of CCK-8 activate magnocellular OT neurons in the SON and PVN as well as parvocellular PVN OT neurons that project into the NTS that may be involved in the gastric signal.

Cisplatin, a widely used anti-cancer drug in chemotherapy, causes various side effects, including nausea/vomiting and anorexia. Previous studies have shown that peripheral administration of cisplatin induces expression of Fos-ir in SON neurons [88]. Arase et al. extended these findings and demonstrated that peripheral administration of cisplatin caused induction of Fos-ir in OT neurons in the SON and PVN in rats [89]. They also demonstrated that mRFP1 fluorescent intensities in the SON and PVN were significantly increased with suppression of feeding behavior after peripheral administration of cisplatin in OT-mRFP1 transgenic rats. Furthermore, intracerebroventricular (ICV) administration of the OTR antagonist (L-368899) abolished cisplatin-induced suppression of food intake at 2 h but not 24 h after intraperitoneal (IP) administration of cisplatin [89]. These results suggest that cisplatin-induced inhibition of feeding may be mediated by the central OT pathway.

### 1.5. Use of OT as a strategy to treat obesity

Obesity and its associated metabolic complications [90-92] increase risk for the development of type 2 diabetes (T2D), sleep apnea, heart disease, many cancers, depression, and COVID-19 related hospitalizations [93-98] and has become a major worldwide health concern [99]. According to the National Health and Nutrition Examination Survey, obesity prevalence (age-adjusted) increased from 30.5% from 1999-2000 to 42.4% in 2017–2018 [100]. Current anti-obesity drugs are either not well tolerated or associated with unwanted and/or adverse side effects (i.e. sleep disturbance, worsening depression, nausea and diarrhea [101-104]), highlighting the need for newer and more effective treatment options. While OT is well recognized for its role in osmoregulation [105], reproductive behaviors [106, 107] and prosocial behavior [108, 109], it also has important roles in energy balance [110-112] and has emerged as a potential adjunct therapy to treat obesity.

Recent studies suggest that combination therapy (i.e. dual-agonist treatment) may be more effective than monotherapy for producing sustained weight loss [[113, 114]] [see [115] for review]. The failure of therapies to induce sustained weight loss in obese humans is thought to occur, in part, by activation of potent orexigenic mechanisms in the brain that increase food intake and reduce energy expenditure, thereby increasing weight regain and preventing further weight loss [116]. Combination drug therapies aimed at both reducing food intake and/or stimulating energy expenditure are likely required as successful weight-loss strategies [115]. The identification of recruitable brown adipose tissue (BAT) in humans [117] has renewed interest in drugs that target BAT to elicit weight loss by increasing energy expenditure, in combination with drugs that decrease food intake.

Currently available FDA-approved weight loss drugs already include combination therapies, such as Qsymia (phentermine + topiramate) and Contrave (bupoprion + naltrexone) [118]. While OT treatment alone has been found to be effective at eliciting weight loss [39, 55, 112, 119-125], these effects appear to be relatively modest after a 4-8 week treatment period in diet-induced obese (DIO) mice [≈ 4.5-4.9% [123, 126]], rats [≈ 4.9-8.7% [123, 127]], nonhuman primates (rhesus monkeys) [≈ 3.3% [55]] and humans with obesity [≈ 9.3% [112]], relative to weight loss achieved in response to long-term treatment (20 weeks to ≥ 1 year) with combination therapies in humans. Combination therapies such as cagrilintide (amylin analogue) + semaglutide, and Qsymia have resulted in ≈ 17.1 and 10.9% weight loss (% of initial body weight), respectively [128, 129].

Notably, OT in combination with other pharmaceutical agents can produce sustained reductions of consumption of highly palatable food (high-fat/high-sugar diet) and elicit weight loss. The combined treatment of OT (fourth ventricular infusion) and the beta-3 receptor agonist, CL 316243 (repeated 1x daily IP injection), was effective at eliciting greater weight loss (15.5%) compared to OT (7.8%) or CL 316243 (9.1%) alone [127]. These effects were associated with transient reductions of energy intake, decreased adiposity, adipocyte size and increased BAT thermogenesis and browning of epididymal white adipose tissue. These findings are consistent with the effects of other beta-3 receptor agonists [including L-755507, CL-316243 and the FDA-approved beta-3 receptor agonist, mirabegron] to increase energy expenditure [130-133] and BAT thermogenesis [127, 130, 131, 134] in nonhuman primates (rhesus monkeys) and humans. However, there is controversy over whether doses of beta-3 receptor agonists that increase energy expenditure, BAT thermogenesis and elicit weight loss also elevate heart rate and blood pressure [131, 134-138]. While it is important to note that adverse cardiovascular effects (heart rate or blood pressure) have not been reported following administration of the lowest dose of mirabegron (50 mg; [134, 136]) that is FDA-approved for overactive bladder, these findings highlight the need for careful monitoring of adverse cardiovascular effects when this particular beta-3 receptor agonist. Edwards and colleagues recently reported that chronic treatment with OT and the beta-3 agonist, CL 316243, produces additive reductions of body weight in DIO rats, at a dose of CL 316243 not found to adversely impact heart rate in lean rats [139]. While future studies should confirm that this particular dose of CL 316243 fails to elicit adverse effects on heart rate in DIO rats, our findings raise the possibility that lower doses of the beta-3 agonists may be used in combination with OT to generate

additive effects on weight loss while minimizing potential negative side effects associated with sympathomimetics [140].

OT and the opioid antagonist, naltrexone, is another drug combination that has been used successfully to reduce food intake and/or treat obesity in animals and humans. The effectiveness of this treatment might be due, in part, to the finding that opiate antagonists increase the release of OT [141, 142] and potentiate the effects of OT [143]. A recent study by Hsu and colleagues found that chronic intranasal OT, in combination with the opioid antagonist, naltrexone, reduced food intake and elicited weight loss in an adolescent boy with hypothalamic obesity following craniopharyngioma tumor resection [110]. Head and colleagues extended this study further and found that OT and naltrexone act synergistically to reduce intake of a high-fat/high-sugar diet over a 24-day period [53] in rats at doses that produce changes in gene expression of several genes in both homeostatic and feeding reward centers of the brain. Collectively, these findings suggest that OT in combination with other weight loss agents, can achieve greater weight loss than either treatment given alone.

One advantage to the incorporation of OT with other anti-obesity treatments is that OT appears to act through multiple mechanisms to elicit weight loss-which may explain why it is able to maintain weight loss despite a waning in its effectiveness to reduce food intake over time [39, 119, 121, 123, 126, 127]. In contrast, CL 316243, when given by systemic infusion in mice, has been found unable to produce long-term reductions of body weight [144]. This effect appears to be driven, in part, by an inability to produce sustained reductions of food intake, which can be a limiting factor with this drug as a monotherapy, depending on route of administration and dosing [144]. Previous studies raise the possibility that chronic OT treatment may prevent the drop of energy expenditure that occurs in the setting of prolonged reductions of food intake and weight loss [145-149]. Thus, OT may serve as a useful adjunct to help offset counter-regulatory mechanisms that occur in response to weight loss that would normally increase food intake and reduce energy expenditure to promote weight gain.

## 2. Challenges and perspectives

While the vast majority of studies thus far has shown OT as a promising potential tool in our efforts to combat obesity and overeating, there are also clear gaps in our understanding of how OT affects energy balance and metabolism. Furthermore, there are certain aspects of OT's action – some stemming from the pleiotropic action of this neuropeptide while others from the chronicity of exposure to OT - that necessitate additional work in order to refine OT treatments to maximize their effectiveness. It is important to note that one common concern about studies that have examined the effectiveness of OT to reduce food intake (particularly those following peripheral administration) is that relatively high doses are often used [150, 151] which may be produce off-target effects (including action at vasopressin receptors). Finally, the ability of the exogenous OT molecule and synthetic OT receptor ligands to reach specific targets, especially within the brain, poses one of the greatest challenges in OT pharmacology.

In the context of using OT as a strategy to treat obesity, the majority of clinical trials have only examined the effects of OT treatment for a relatively short duration of exposure (up to 8 weeks). In addition, not all studies have reported an effect of intranasal OT to reduce food intake-most recently [152]-for reasons that are not entirely clear (for review see [153, 154]). Remaining challenges will be to determine the safety, efficacy and tolerability of chronic OT administration (IN) in humans with obesity as well as to optimize dose and frequency of administration to achieve clinically meaningful weight loss in the absence of adverse or unwanted side effects [110, 112, 155-157]. In addition, it would be helpful to examine the long-term use of OT as an effective weight loss therapeutic in female DIO nonhuman primates and adolescents with obesity. Long-acting selective OT agonists have been developed and found to be effective at evoking weight loss and/or reducing weight gain in overweight or obese rodent models [158-161] but such compounds are in their early stages and will need to be validated as safe and effective tools in non-human primates and humans. One key advantage is that longer acting and more selective OT analogues could be safer and given less frequently to help reduce the burden and potential adherence or tolerability issues that may be associated with having to administer IN OT up to 4x/day over an 8-week period in order to elicit weight loss [112] or adiposity [162]. Future studies will need to take into account the possibility that chronic OT treatment may also produce adverse cardiovascular effects [159, 163, 164] through interactions with vasopressin receptors [159], hyponatremia [164, 165], or down-regulate OTRs within the CNS [166-168], increase anxiety [168, 169], aggression [170], change partner preference [171] and/or cause feelings of distrust in humans with borderline personality disorder [172] (see [150, 173, 174] for review). It should not be neglected that central OT may have bi-modal aspects of physiological role on regulation of feeding/body weight and pathophysiological role on nausea/vomiting and anorexia. Although rats are unable to vomit, nausea may cause inhibition of feeding [175].

It is possible that in chronic scenarios, we might be able to rely on the endogenous OT system's activation to promote select metabolic effects. For example, contrary to the transient effects of CCK and secretin, activation of central insulin receptors by peripheral insulin appears to induce a long-lasting activity of OT systems that may exert long-term effects. In line with this, data from a human study reveals that patients suffering from metabolic syndrome – a condition characterized by high insulin levels – exhibit higher serum OT concentrations than control subjects. Since most of the experiments have been conducted in anesthetized rats and *in vitro* settings, further studies await to test whether this insulin effect is preserved in conscious animals and humans in both normal and pathological conditions. In addition, it remains to be determined whether the activation of OT systems by insulin results in somatodendritic (central) OT release that may act on distant targets within the brain.

As described in detail above, what offers us hope in that OT may serve as a good tool for curbing overconsumption of diets commonly encountered in the obesogenic environment (i.e., most detrimental to excessive body weight) is evidence suggesting that OT reduces food motivated behaviors. It involves an inhibition in dopamine neuron activity in response to Pavlovian cues associated with sucrose access in the VTA [64]. One should note, however, that the oxytocinergic projections to the VTA play a critical role in mediating (and

parsing) other rewarding behaviors, including prosocial behavior. Without oxytocinergic input to the VTA social behavior is mitigated [46], thus suggesting that the impact of OT on VTA dopamine responses is dependent on the nature of the reward. For example, it is possible that OT reduces food intake in part due to increasing the motivation for non-feeding behaviors. Thus, palatable food becomes less tempting in favor of socializing, mating, or other types of behaviors (reviewed in [176]). In line with that, an i.p. OT receptor antagonist increases sucrose intake in subordinate mice in the absence of dominant mice, but unexpectedly reduces sucrose intake in the presence of dominant mice. However, in dominant mice, injection with an i.p. OT receptor antagonist reliably increases sucrose intake regardless of social setting. NAcc-infused OT decreases episodic intake of energy dense standard chow as well as energy-dilute or noncaloric palatable sweet solutions (both sucrose and saccharin) in rats housed alone [49]. However, when rats are placed in cages that allow for partial social interaction, OT does not affect consumption driven by energy needs or by palatability.

Together, these data suggest that food intake modulation by OT is dependent on social cues, but further data are needed to determine the extent to which these context specific modifications in OT's impact on food intake act via central reward pathways. This pertains to laboratory animal studies, which have mainly relied on solitary feeding paradigms, as well as to clinical studies. To the best of our knowledge, there have been no analyses as to whether sociality affects effectiveness of IN OT in humans, however, one might speculate that the presence of other individuals, the nature of interactions between subjects as well as the transient perception of the value of food offered during the trial may act as significant modifiers.

A significant gap in the literature exists with regard to how OT impacts reward-based eating behavior in females. In females, ICV OT reduces food intake in hyperphagic Sim1 haploinsufficient mice [19], and ICV injections of OT reduce food intake in females though the dose response curve is slightly shifted toward requiring higher doses [177]. Notably, the elevated doses required are largely explained by a reduced effectiveness of OT to reduce food intake during the pro-estrus stage of the estrus cycle, an effect that is attributable to the estrogen surge at that time [177]. Similarly, peripheral OT treatment in mice on a HFD reduced food intake and body weight, but food intake reductions due to OT occurred over more days in males than in females, suggesting a potentially blunted anorexigenic response to OT in females [120]. In humans, OT reduces post-prandial intake of snacks in a manner similar to males [63]. Little is known about the impact of OT on food motivated behaviors, reward circuitry, competing motivations, or inhibitory control, and therefore this area represents an important direction for future research.

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## Data Availability Statement

The present article is a mini-review that does not report any unpublished data.

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