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Current findings on the role of oxytocin in the regulation of food intake

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Highlights

- The hypothalamic neuropeptide oxytocin acts as an anorexigenic signal.
- Intranasal oxytocin delivery curbs food intake in healthy and obese individuals.
- Possible links to oxytocin's psychosocial function are discussed.
- Does oxytocin hold some clinical potential as an appetite-reducing drug?

Abstract

In the face of the alarming prevalence of obesity and its associated metabolic impairments, it is of high basic and clinical interest to reach a complete understanding of the central nervous pathways that establish metabolic control. In recent years, the hypothalamic neuropeptide oxytocin, which is primarily known for its involvement in psychosocial processes and reproductive behavior, has received increasing attention as a modulator of metabolic function. Oxytocin administration to the brain of normal-weight animals, but also animals with diet-induced or genetically engineered obesity reduces food intake and body weight, and can also increase energy expenditure. Up to now, only a handful of studies in humans have investigated oxytocin's contribution to the regulation of eating behavior. Relying on the intranasal pathway of oxytocin administration, which is a non-invasive strategy to target central nervous oxytocin receptors, these experiments have yielded some promising first results. In normal-weight and obese individuals, intranasal oxytocin acutely limits meal intake and the consumption of palatable snacks. It is still unclear to which extent – or if at all – such metabolic effects of oxytocin in humans are conveyed or modulated by oxytocin's impact on cognitive processes, in particular on psychosocial function. We shortly summarize the current literature on oxytocin's involvement in food intake and metabolic control, ponder potential links to social and cognitive processes, and address future perspectives as well as limitations of oxytocin administration in experimental and clinical contexts.

Keywords

Oxytocin, intranasal administration, central nervous system, brain, metabolism, food intake, eating behavior, glucose homeostasis, cognitive processes, psychosocial function, obesity.

Contents

1. Introduction

The hypothalamic neuropeptide oxytocin, besides its physiological function in parturition and lactation, is primarily known for its role in psychosocial and affective processing, e.g., in bonding behavior, emotion regulation, and sexual function [1–4]. Oxytocin is released into the circulation by axonal terminals in the posterior pituitary and, in addition, acts directly on central nervous receptors. Interestingly, oxytocin is produced in hypothalamic regions that also regulate appetite and metabolism and are targets of appetite-regulating hormones like leptin, cholecystokinin (CCK) and ghrelin [5,6]. Important insights into the role of oxytocin in the central nervous regulation of metabolic functions have been obtained in animal experiments (e.g., [7–9]; for review see [10,11]) which indicate that oxytocin contributes to the control of food intake, energy expenditure and glucose homeostasis [12,13]. In recent years, first experiments to investigate respective effects in the human organism have been performed, primarily relying on the intranasal pathway of neuropeptide delivery to the brain. Intranasal administration of oxytocin in humans has been repeatedly shown to inhibit eating behavior driven by hunger due to energy depletion as well as by more reward-related, 'hedonic' factors associated with food intake [14–16]. This short review summarizes the effects of oxytocin on ingestive behavior in healthy humans and subjects with obesity or eating disorders, with the aim of providing an update on current research and future directions, and looks at possible links between oxytocin's eating-related function and its role in psychosocial regulation (see Figure 1 for an overview of oxytocin effects).

2. The neuropeptide oxytocin

Oxytocin is a nine-amino acid neuropeptide hormone that is predominantly produced in two hypothalamic regions, the paraventricular nucleus (PVN) and the supraoptic nucleus [17]. PVN oxytocin neurons project to the pituitary gland (about 40%) and a number of brain areas

including the brainstem. Around ten percent of PVN neurons project to three core areas of the brainstem that play an important role in the regulation of food intake: nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve (DMNV), and area postrema [18,19]. Oxytocin in addition is active in brain areas of relevance for reward- and eating-related behavior such as the ventral tegmental area (VTA), nucleus accumbens (NAcc), and nucleus stria terminalis [20]. It is assumed that only a small ratio of oxytocin released into the periphery via the posterior pituitary passes the blood-brain barrier to re-enter the brain [21], which might explain why oxytocin concentrations are up to 1000 times higher in the brain than in the blood. In conjunction with the observation that the half-life of the peptide in the central nervous system (CNS) is over three times longer than in the periphery (19 vs. 6 minutes) [22,23], this pattern furthermore points to the specific relevance of the hormone for central nervous functions [24].

The role of oxytocin in the periphery and in particular in the female reproductive system is well established, first of all with regard to fertilization and parturition. During pregnancy, the uterus increases its oxytocin sensitivity before giving birth, and receptor density increases during labor [25]. The human ovary also expresses oxytocin receptors (OXTR), and oxytocin possibly affects the fertilization process and the very early development of the embryo [26]. The most prominent role of oxytocin in humans concerns lactation. The infant triggers secretion of the peptide by sucking on the mother's nipple, which stimulates additional milk ejection. The male reproductive system has also been observed to be oxytocin-sensitive [27].

The G-protein coupled OXTR [28] can be found in a wide range of brain regions (see ref. [27,29] for review), e.g., in hypothalamus, amygdala, anterior cingulate cortex, olfactory nucleus, and in limbic areas [30]. Moreover, oxytocin interacts with other neurotransmitters to influence brain function. It has been suggested that serotonin increases oxytocin

concentrations [31] and that dopamine interacts with oxytocin [32] to modulate activity of the brain's reward circuitry [32,33] (see also chapter 4.2 of this review). The latter interaction has been assumed to be of relevance for behavioral disorders such as sexual dysfunction, autism, depression, but also eating disorders (see ref. [34] for further reading). In addition to its expression in the brain, oxytocin is expressed in myenteric and submucous ganglia and nerve fibres of the human gastrointestinal tract [35], with potential consequences for eating behavior and metabolism.

A suitable way to study the contribution of (neuro)peptidergic messengers to human brain function is the intranasal route of administration, which largely bypasses the blood-brain barrier (BBB) and delivers neuropeptides directly to the CNS. In humans, intranasally administered peptides have been found to reach the CNS within 45 min after delivery [36]. Since intra-neuronal transport of neuropeptides from the nasal mucosa to the olfactory bulb normally takes several hours [37], it is assumed that intranasally administered neuropeptides travel to the CNS via extra-neuronal pathways, bypassing the BBB paracellularly by diffusing into the subarachnoidal space across the olfactory epithelia and through intercellular clefts between sustentacular cells and olfactory neurons [38]. Passage of intranasally delivered peptides to the brain may also be established along cranial and trigeminal nerve branches [39]. Most recently, bulk flow within the perivascular space of cerebral blood vessels has been identified as another transport mechanism after intranasal administration [40]. Research relying on nasal spray application (mainly of 24-30 IU) of oxytocin indicates that the concentration of the peptide increases in both saliva and peripheral blood, with peak plasma concentrations at 10-40 min, or even 90 min following intranasal application [41–43]. Recent experiments by Striepens and colleagues [44] suggest that plasma oxytocin concentrations peak 15 min after intransal adminstration (24 IU) while cerebrospinal fluid oxytocin concentrations reach their maximum up to 75 min post administration, so that the

strongest brain effect of intranasal oxytocin might emerge around 60 min after administration. Intranasally administered oxytocin has been assumed to travel along the olfactory system to amygdaloid nucei, which are directly connected to the hypothalamus. This projection also influences the ventral striatum, an essential part of the reward system, with potential modulatory effects on forebrain structures [20] including cingulate and other parts of the frontal cortex [45]. It should be added that although intranasal delivery of oxytocin is an easy-to-use and generally well-tolerated approach [46,47], routine use, in particular in clinical settings, will necessitate some optimizing with regard to absorption despite degradation by the nasal mucosa (for review see [48]). In this context, the respective administration mode appears to be relevant considering recent reports that the administration of nebulized or aerosolized compared to simple spray solutions of oxytocin may permit CNS-specific uptake of the hormone [49,50].

3. Oxytocin's impact on cognition and emotion

The role of oxytocin in psychosocial, cognitive and emotional processes has become increasingly clear in recent years (see ref. [3,51] for reviews). A rapidly growing number of studies provides evidence that intranasally administered oxytocin enhances empathy [52], the perception of emotional facial expressions as well as covert attention to happy faces [53–56] and increases trust in others [2]. Oxytocin also enhances the recognition of emotional states expressed in body language [57], the formation of social memory contents, respective memory performance [58,59], and moreover may even promote self-perception [60]. However, oxytocin's effects may not be purely beneficial in a social sense since the hormone can also trigger aggression towards members not belonging to one's own group (out-group vs. in-group effects) and increase in-group favoritism [61,62](see [63] for review). Neural mechanisms behind behavioral effects of oxytocin have been identified in studies using

functional magnetic resonance imaging (fMRI; see [64] for review). One of the first studies to examine the effect of oxytocin on neural responses found that the hormone reduces amygdala activation in response to fear-inducing stimuli [65]. Domes and coworkers [66] reported amygdala responses to facial stimuli to be suppressed by oxytocin independent of emotional valence, and suggested that oxytocin is involved in general emotion regulation. In accordance with this assumption, the impact on amygdala activity of the perception of emotional (happy and angry) faces, and also of pain, trust and hearing infant laughter [67–70] turned out to be modulated by oxytocin. In addition, oxytocin affects the activity of frontocortical areas such as anterior cingulate cortex, orbitofrontal cortex and ventromedial prefrontal cortex during the observation of emotional faces [67,71].

Social context is an important modulator of the effects that oxytocin exerts on the processing of social-emotional stimuli. During exposure to aversive social stimuli amygdala activity is inhibited by oxytocin whereas insular activity is increased along with functional coupling to the amygdala [72]. This pattern suggests that oxytocin has anxiogenic effects when subjects are confronted with (socially) threatening stimuli [73–75] and may support the formation of memory for social interactions [76]. Fittingly, increases in saliva and, respectively, plasma concentrations of oxytocin have been found during psychosocial stress [77] and relational distress [78]. In contrast, oxytocin improves the positive effect of social support on stress reactions and, in these circumstances, exerts anxiolytic effects [74,76,79]. Person variables moreover appear to play an important role in the interplay between oxytocin and the regulation of anxiety and stress [74,80].

Oxytocin has also been implicated to contribute to memory function. In recent animal studies, oxytocin was found to protect hippocampus plasticity against stress [81] and to enhance the formation of hippocampus-dependent memory [82]. The hippocampal formation is essential for the formation and storage of declarative memory, i.e., memory for facts and

events that can be consciously recollected [83]. Mice lacking oxytocin display impairments in social memory function, failing to recognize animals they have been familiarized with [84]. In contrast, other animal studies suggest oxytocin-induced impairments in memory and learning [85]. In humans, the peptide has been linked to social recognition, inasmuch as it strengthens the encoding of facial features [86]. On the other hand, Herzmann and coworkers [87] found that oxytocin impairs recognition memory for both socially relevant and irrelevant objects. In related studies, Heinrichs and colleagues [88] observed impaired recall performance after intranasal oxytocin administration. In a recent review of the effects of intranasal oxytocin on long-term memory in humans, Brambilla and colleagues [89] therefore point out that there is a link between oxytocin and memory performance, but that the nature of this effect and the respective mechanisms are still unclear. It has even been proposed that the effects of oxytocin on social behavior might be primarily due to its impact on global cognitive processing capacities, namely improvements in working memory [90].

The psychosocial effects of oxytocin shortly summarized above may be of particular clinical relevance with a view to psychiatric disorders with a pronounced social component. Therefore, the clinical potential of oxytocin administration has been investigated with regard to disorders involving social dysfunction such as autism, social anxiety, borderline personality disorder and schizophrenia as well as to impairments like post-traumatic stress disorder (for review see ref. [91]). Respective meta-analyses indicate that improving effects of oxytocin may be particularly pertinent in autistic persons (see ref. [92] for an overview). At the same time, there is some concern and discussion about the use of intranasal oxytocin in behavioral research [93–98], in particular about the efficacy of oxytocin penetration into the brain after intranasal administration [93]. Walum and colleagues [99] recommend improving the reliability of human studies using the intranasal administration paradigm. Publication bias might be an issue, so that better dissemination of oxytocin studies with

negative results appears desirable [98]. Clearly, a greater number of positive as well as negative results is needed to understand the complex effects of intranasal oxytocin on human behavior and to unravel the possible mechanisms behind these effects.

4. Oxytocin as an anorexigenic neuropeptide

4.1. Oxytocin's impact on eating behavior and energy homeostasis in animals

Thanks to research efforts in the past two to three decades, the contribution of oxytocin to the regulation of eating behavior and metabolism has gained increasing attention, and it seems like oxytocin is now not only recognized as a social peptide, but also as a messenger with relevance for food intake control. First hints at a role of oxytocin in the regulation of food intake came from animal studies where lesions of the oxytocin-expressing hypothalamic PVN resulted in increases in food intake and body weight [100,101]**.** In 1989, Arletti and colleagues [102] demonstrated that intraperitoneal (IP) and intracerebroventricular (ICV) injection of oxytocin decreases chow intake in male rats one hour after administration. Further experiments indicated that ICV administration of oxytocin reduces food intake in normal-weight rats [7]. Importantly, animals with genetically or diet-induced obesity (DIO) also respond to oxytocin administration. Thus, IP and subcutaneous (SC) injection of oxytocin suppresses food intake and SC injection reduces fat mass in DIO mice [8], and also improves insulin sensitivity [103]. In ob/ob mice, two weeks of SC oxytocin administration led to a reduction in food intake and body weight [104]. In obese Zucker-fatty rats [105] and obese diabetic db/db mice [106], ICV and, respectively, IP oxytocin administration also produced anorexigenic effects. Fittingly, twelve weeks of SC oxytocin administration via osmotic pumps improved glucose metabolism and reduced body fat content in db/db mice [107]. Corresponding anti-obesity effects of oxytocin were found in DIO rats [12,108]. Notably, oxytocin- or OXTR-deficient mice display modest, late-onset obesity in the absence

of changes in food intake behavior [109,110], and in some experiments oxytocin did not alter energy intake but still improved energy homeostasis by increasing lipolysis [108]. Enhancing effects on energy expenditure have moreover been observed to mediate some of the catabolic impact of oxytocin [9,12,13,111]. Thus, the beneficial effect of oxytocin on body weight regulation as derived from animal studies is clearly not limited to reductions in food intake.

The inhibitory effect of oxytocin on food intake has been attributed to different mechanisms in which the peptide appears to be involved, varying between homeostatic and more reward-related, hedonic processes. Oxytocin delays gastric emptying [35], while gastric distention activates oxytocin release [112]. In addition, oxytocin has been found to influence food selection [113,114] (see ref. [115] for review). Animal studies moreover suggest that oxytocin in particular decreases carbohydrate intake. Oxytocin-knockout mice display increased intake of sucrose [116] and also increased carbohydrate intake in general, i.e., independent of sweet taste [113]. Vice versa, injection of oxytocin into the VTA suppresses sucrose intake [117]. Experiments distinguishing between the sweet and the fatty component of palatable food show that oxytocin deficiency seems to affect carbohydrate rather than fat consumption [114,118]. However, comprehensive research by the group of Blevins [119] indicates that long-term third ventricular oxytocin infusion also affects fat consumption and fat oxidation: in rats kept on a high-fat diet, oxytocin curbed calorie consumption and decreased body weight gain relative to controls, effects that were not observed when the rats were on a chow-diet. Importantly, oxytocin also reduced energy intake and prevented weight gain in animals on a sucrose-free high-fat diet. In sum, these experiments indicated that oxytocin maintains energy expenditure despite concurrent weight loss, increases fat oxidation and may boost CCK-mediated satiety responses [11]. The ability of oxytocin to sensitize satiety centers in the hindbrain to the effects of CCK can be assumed to play a role in this context [6].

The anorexigenic role of oxytocin has been proposed to rely at least in part on the downstream mediation of the effects of leptin [120], a hormone produced in white fat cells that provides the CNS with feedback on the amount of energy stored as body fat and therefore is one of the major signals establishing energy balance [121]. Blevins and coworkers demonstrated in rats that oxytocin-expressing neurons in the hypothalamic PVN contribute to the inhibitory impact of leptin on food intake [5]. Wu and coworkers [13] found no effect of adult ablation of oxytocin neurons on body weight, food intake and energy expenditure in mice on a regular diet; still, the mice lacking oxytocin neurons showed a reduced response to the anorexigenic effect of leptin and were more prone to develop DIO due to reduced energy expenditure. Hypothalamic oxytocinergic neurons project to structures of the brain reward circuit such as the NAcc [122], and oxytocin administration attenuates dopamine signaling in the NAcc as well as the striatum [123], which suggests that the peptide may also inhibit eating behavior by modulating the reward-related, 'hedonic' effect of eating (see also next paragraph).

4.2. Oxytocin's impact on the control of food intake in healthy humans

Studies in humans on the effects of oxytocin on eating behavior are still rare. Early studies failed to demonstrate an effect of peripheral administration of oxytocin on food intake [124], which is not surprising since, as stated above, only a small percentage of oxytocin (presumably around 0.005%) may cross the blood-brain barrier to bind to oxytocin receptors in the CNS [21]. However, the results of more recent studies relying on the intranasal administration of oxytocin have yielded first evidence for a hypophagic effect of the peptide. The first study addressing the impact of intranasal oxytocin on food intake investigated if the peptide reduces hunger- and reward-driven food intake in normal-weight healthy men [14]. It turned out that oxytocin strongly decreased the consumption of chocolate cookies assessed around three hours after peptide administration and 90 min after ad-libitum breakfast intake,

i.e., at a time-point when reward-related eating motivation prevailed. In contrast, hunger-driven breakfast intake in the fasted state was not affected by oxytocin [14]. In that study, in accordance with experiments in humans [79] and animals [12,108], intranasal oxytocin also suppressed endocrine stress axis activity and curbed the postprandial peak in plasma glucose concentrations. Beneficial effects on glucose homeostasis were corroborated in experiments in healthy men who underwent an oral glucose tolerance test [125]. Here, oxytocin attenuated peak excursions of plasma glucose and augmented early increases in insulin and C-peptide concentrations, results that according to oral minimal model analyses indicated a pronounced oxytocin-induced increase in β-cell responsivity and a more than twofold improvement in glucose tolerance. When the impact of oxytocin on eating behavior was compared between normal-weight and obese subjects [16], cookie intake turned out to be likewise reduced by oxytocin and the peptide induced comparable changes in stress hormone- and glucose homeostasis-related blood parameters in obese participants. Remarkably, obese individuals in addition decreased hunger-driven breakfast intake after oxytocin administration, i.e., displayed a hypophagic effect that was absent in normal-weight humans. However, oxytocin-induced reductions in hunger-driven food intake from a breakfast buffet were found in obese, but also normal-weight participants in related studies [15], which moreover indicated that the anorexigenic effect centered on fat intake (before correction for multiple comparisons). These results were accompanied by an oxytocin-induced increase in circulating CCK concentrations that, as the authors report, were not related to changes in calorie intake, and signs of improved insulin sensitivity after administration of the peptide.

It is to note in this context that oxytocin and dopamine signaling have been found in humans [126] and animals [127] to interact in the regulation of pair bonding, and that intranasal oxytocin administered to nulliparous and postpartum women (at the dose also used in food-related experiments [14–16]) increases VTA activation during exposure to images of

crying infants as well as sexual stimuli [128]. Likewise, oxytocin enhances VTA activation in response to cues that signal social reward or punishment, although this effect is modulated by intraindividual differences in sociability [129]. Moreover, variability in the oxytocin gene explains interindividual differences in dopaminergic responses to stress measured by positron emission tomography [130]. These findings support the tentative assumption that oxytocin exerts some of its effects on food intake in humans by acting on reward processing, although at the moment it remains to be seen if the effect of oxytocin on eating behavior is primarily hunger- or reward-driven.

There is some first evidence that in addition to acting via homeostatic and reward-related mechanisms, oxytocin also reduces food intake by enhancing cognitive control mechanisms. Thus, a recent neuroimaging study [131] revealed that oxytocin reduces craving for food and in parallel increases activity of prefrontal cortical areas in women. Clearly, further studies are needed to pinpoint the exact mechanisms behind the hypophagic effect of oxytocin in humans. They should also answer the obvious question whether this effect is conveyed, at least in part, via oxytocin's contribution to the regulation of psychosocial functions, so that a strong modulatory role of social context in the extent or even direction of oxytocin's effect on eating behavior would be expected (see chapter 5).

4.3 Oxytocin as a potential intervention in eating disorders and obesity

The contribution of oxytocin to the control of food intake as illustrated in studies in animals and healthy subjects raises the question if oxytocin might support therapeutic interventions aimed at specific eating disorders. Individuals with anorexia nervosa have been found to display increased oxytocin concentrations after standardized meal intake [132], suggesting that changes in oxytocin signaling might be a feature of or even a pathophysiological factor in this disorder. Accordingly, anorexia has been associated with epigenetic dysregulation of the OXTR gene [133]. Intranasal oxytocin administration to patients with anorexia nervosa

changes their attitude towards social and food-related stimuli; the peptide induces a shift from the avoidance of angry faces towards increased vigilance and moreover attenuated attention to food stimuli [134,135]. These and related promising findings [136,137] by the group of Janet Treasure suggest that therapeutic approaches aiming at improving emotional and eating-related processes in anorectic, and moreover bulimic patients might be supported by concurrent oxytocin delivery [138], but will need to be corroborated in larger clinical trials. Of note, irregularities in oxytocin signaling, i.e., an OXTR gene polymorphism, have also been associated with bulimia nervosa [139].

Obesity is presumably linked the emergence of central nervous resistance against the hypophagic effects of the adiposity signals leptin and insulin [121,140]. As mentioned above, it appears that in some contrast to this pattern the brain of obese animals and humans displays intact or even enhanced sensitivity to the anorexigenic impact of oxytocin [16,120]. It has been speculated that the relatively elevated cholesterol levels in obesity may boost high-affinity binding of oxytocin to the OXTR [27,141]. Support for the assumption that oxytocin signaling is altered in obesity comes from studies linking the OXTR gene to body weight [142,143] and the observation that overweight subjects as well as newly diagnosed diabetic patients display lower circulating concentrations of oxytocin when compared to normal-weight controls [144]. Patients with Prader-Willi syndrome, who suffer from hyperphagic obesity as a consequence of persistent food craving, display a 40% reduction in the number and size of oxytocin neurons [145]. Pilot experiments in patients with this syndrome who received oxytocin substitution via the intranasal pathway for eight weeks yielded none of the intended effects on body weight and psychosocial function, which might have been due to a lack of feed-forward endogenous oxytocin release after exogenous delivery [146]. In related studies [147], young children with Prader-Willi syndrome improved their social and food-related behavior after a four-week oxytocin intervention. Taken together, these findings

suggest that the oxytocin system might be a potential target of clinical interventions to normalize eating behavior [16,46]. Considering evidence that metabolic disorders increase the risk of cognitive impairments [148,149] and meta-analyses indicating that weight loss in subjects with overweight or obesity is associated with respective enhancements [150], the beneficial metabolic effect of oxytocin may even be associated with improvements in cognitive processes.

In animal experiments, DIO rhesus monkeys receiving subcutaneous oxytocin for four weeks reduced their food intake by around 27% and their body weight by 3.3%, while their energy expenditure increased by 14% [9]. Obese human subjects reduced their food intake by around 10% in the first hours after acute intranasal administration [16]. When obese individuals received four daily intranasal doses of 24 IU oxytocin for a duration of eight weeks, they were observed to lose around 9 kg of body weight and to show a decrease in waist and hip circumference [103]. Since the interpretation of these results is complicated by the large pre-administration differences in BMI and age between the treatment and the control groups (36 vs. 30 kg/m^2, 29 vs. 41 years), further and possibly larger trials are clearly needed to sound the potential of oxytocin as an anti-obesity drug. In these studies it will be of high relevance to address potential sex differences, which are suggested by some experiments in animals [13], and carefully control for side effects on metabolic parameters but also psychosocial functions. Although the intranasal administration of oxytocin at doses from 18-40 IU – the range that comprises most doses commonly applied in experimental settings – does not acutely induce distinguishable side-effects according to meta-analyses [47] chronic oxytocin administration was associated with detrimental effects on social behavior in a number of animal studies [151–153]. While it is unclear whether these findings can be directly translated to the human situation, they pose a certain caveat to respective clinical trials [154].

5. Oxytocin as a link between psychosocial mechanisms and eating behavior

The findings discussed above open up an interesting new perspective for oxytocin as a regulator of eating behavior in humans, although the mechanisms underlying oxytocin's hypophagic effect are only poorly understood. In particular, it is unknown why oxytocin in contrast to other satiating messengers is effective in obese humans. It might even be proposed that the impact of oxytocin on eating behavior is tightly interrelated with or even dependent on its psychosocial function, so that a specific social setting of food intake could be a necessary prerequisite for the effects of oxytocin to emerge. Notably, animal experiments indicate that social cues can modulate the effect of an OXTR antagonist on sucrose intake: subordinate mice only showed increased sucrose consumption due to OXTR antagonization when no social cues related to a dominant animal were present [115,155]. It is well-known that in humans, cognitive factors such as long-term dietary goals [156], social norms [157] and the context of eating, e.g., time of the day [158], are of paramount relevance for everyday food intake behavior. They may even override the homeostatic/reward-related control of ingestion [159]. In particular, the social context of food intake is a strong determinant of how much is consumed. Meals that are eaten in the company of others are larger than meals eaten alone [160], and the duration of meals is prolonged when more people are present [161]. The amount of ingested food also tends to follow the example given by other subjects – regardless if they are present or respective information is given [162] – but this effect appears to be triggered only by peers of the same weight status [163]. Obese individuals model their food intake according to other obese but not to normal-weight subjects [164]. Importantly, the oxytocin effects on eating behavior found in laboratory studies [14–16] were observed in people eating alone – albeit under overt or implicit supervision by the experimenters – whereas in everyday life, most meals are ingested in social settings.

Considering the involvement of oxytocin in psychosocial function [165], oxytocin's effect on food intake in humans might indeed be strongly modulated or even primarily mediated by "non-physiological" (in the sense of predominantly psychological) factors. This assumption is supported by studies in chimpanzees where active food sharing increased urinary oxytocin levels and bonding behavior [166]. Moreover, oxytocin's attenuating effect on stress reactivity and food consumption might be argued to converge with its basic physiological role in pair-bonding and mother-infant-interaction. E.g., the act of breastfeeding certainly benefits from relative protection against interfering (food-related) stimuli from the environment. In this regard, social context and interindividual differences as modulators of psychosocial stress [74] can be expected to interact with the effect of oxytocin on eating behavior, but to our knowledge, these interactions are yet to be systematically investigated. Elucidating presumable neuro-psychosocial mechanisms of oxytocin's metabolic impact will be an essential step in the assessment of oxytocin's potential as an appetite-reducing drug under conditions of day-to-day eating behavior. In clinical contexts, the involvement of oxytocin in multiple bodily and psychological functions will demand particular attention because this neuropeptide may also link seemingly unconnected pathophysiological conditions.

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Figure 1. Schematic overview of oxytocin effects. The role of endogenous (primarily hypothalamus-derived) oxytocin has been investigated in numerous studies relying mostly (in the human setting) on intranasal delivery. Oxytocin has been shown to curb food intake and decrease body weight both in animals and humans (purple arrow). Effects on metabolism furthermore comprise increases in energy expenditure, lipolysis, glucose tolerance and insulin sensitivity (green arrow). The psychosocial effect of oxytocin concerns social, emotional and cognitive functions as well as anxiety- and stress-related processes (blue arrow).