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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.

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Acknowledgments

References

1 **1. Introduction**

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

21

22 **2. The neuropeptide oxytocin**

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

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

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

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

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

58 A suitable way to study the contribution of (neuro)peptidergic messengers to human
59 brain function is the intranasal route of administration, which largely bypasses the blood-
60 brain barrier (BBB) and delivers neuropeptides directly to the CNS. In humans, intranasally
61 administered peptides have been found to reach the CNS within 45 min after delivery [36].
62 Since intra-neuronal transport of neuropeptides from the nasal mucosa to the olfactory bulb
63 normally takes several hours [37], it is assumed that intranasally administered neuropeptides
64 travel to the CNS via extra-neuronal pathways, bypassing the BBB paracellularly by
65 diffusing into the subarachnoidal space across the olfactory epithelia and through intercellular
66 clefts between sustentacular cells and olfactory neurons [38]. Passage of intranasally
67 delivered peptides to the brain may also be established along cranial and trigeminal nerve
68 branches [39]. Most recently, bulk flow within the perivascular space of cerebral blood
69 vessels has been identified as another transport mechanism after intranasal administration
70 [40]. Research relying on nasal spray application (mainly of 24-30 IU) of oxytocin indicates
71 that the concentration of the peptide increases in both saliva and peripheral blood, with peak
72 plasma concentrations at 10-40 min, or even 90 min following intranasal application [41-43].
73 Recent experiments by Striepens and colleagues [44] suggest that plasma oxytocin
74 concentrations peak 15 min after intranasal administration (24 IU) while cerebrospinal fluid
75 oxytocin concentrations reach their maximum up to 75 min post administration, so that the

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

88

89 **3. Oxytocin's impact on cognition and emotion**

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

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

111 Social context is an important modulator of the effects that oxytocin exerts on the
112 processing of social-emotional stimuli. During exposure to aversive social stimuli amygdala
113 activity is inhibited by oxytocin whereas insular activity is increased along with functional
114 coupling to the amygdala [72]. This pattern suggests that oxytocin has anxiogenic effects
115 when subjects are confronted with (socially) threatening stimuli [73–75] and may support the
116 formation of memory for social interactions [76]. Fittingly, increases in saliva and,
117 respectively, plasma concentrations of oxytocin have been found during psychosocial stress
118 [77] and relational distress [78]. In contrast, oxytocin improves the positive effect of social
119 support on stress reactions and, in these circumstances, exerts anxiolytic effects [74,76,79].
120 Person variables moreover appear to play an important role in the interplay between oxytocin
121 and the regulation of anxiety and stress [74,80].

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

126 events that can be consciously recollected [83]. Mice lacking oxytocin display impairments in
127 social memory function, failing to recognize animals they have been familiarized with [84].
128 In contrast, other animal studies suggest oxytocin-induced impairments in memory and
129 learning [85]. In humans, the peptide has been linked to social recognition, inasmuch as it
130 strengthens the encoding of facial features [86]. On the other hand, Herzmann and coworkers
131 [87] found that oxytocin impairs recognition memory for both socially relevant and irrelevant
132 objects. In related studies, Heinrichs and colleagues [88] observed impaired recall
133 performance after intranasal oxytocin administration. In a recent review of the effects of
134 intranasal oxytocin on long-term memory in humans, Brambilla and colleagues [89] therefore
135 point out that there is a link between oxytocin and memory performance, but that the nature
136 of this effect and the respective mechanisms are still unclear. It has even been proposed that
137 the effects of oxytocin on social behavior might be primarily due to its impact on global
138 cognitive processing capacities, namely improvements in working memory [90].

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

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

154

155 **4. Oxytocin as an anorexigenic neuropeptide**

156 **4.1. Oxytocin's impact on eating behavior and energy homeostasis in animals**

157 Thanks to research efforts in the past two to three decades, the contribution of oxytocin to the
158 regulation of eating behavior and metabolism has gained increasing attention, and it seems
159 like oxytocin is now not only recognized as a social peptide, but also as a messenger with
160 relevance for food intake control. First hints at a role of oxytocin in the regulation of food
161 intake came from animal studies where lesions of the oxytocin-expressing hypothalamic PVN
162 resulted in increases in food intake and body weight [100,101]. In 1989, Arletti and
163 colleagues [102] demonstrated that intraperitoneal (IP) and intracerebroventricular (ICV)
164 injection of oxytocin decreases chow intake in male rats one hour after administration.
165 Further experiments indicated that ICV administration of oxytocin reduces food intake in
166 normal-weight rats [7]. Importantly, animals with genetically or diet-induced obesity (DIO)
167 also respond to oxytocin administration. Thus, IP and subcutaneous (SC) injection of
168 oxytocin suppresses food intake and SC injection reduces fat mass in DIO mice [8], and also
169 improves insulin sensitivity [103]. In ob/ob mice, two weeks of SC oxytocin administration
170 led to a reduction in food intake and body weight [104]. In obese Zucker-fatty rats [105] and
171 obese diabetic db/db mice [106], ICV and, respectively, IP oxytocin administration also
172 produced anorexigenic effects. Fittingly, twelve weeks of SC oxytocin administration via
173 osmotic pumps improved glucose metabolism and reduced body fat content in db/db mice
174 [107]. Corresponding anti-obesity effects of oxytocin were found in DIO rats [12,108].
175 Notably, oxytocin- or OXTR-deficient mice display modest, late-onset obesity in the absence

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

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

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

215 **4.2. Oxytocin’s impact on the control of food intake in healthy humans**

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

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

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

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

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

268 **4.3 Oxytocin as a potential intervention in eating disorders and obesity**

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

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

284 Obesity is presumably linked the emergence of central nervous resistance against the
285 hypophagic effects of the adiposity signals leptin and insulin [121,140]. As mentioned above,
286 it appears that in some contrast to this pattern the brain of obese animals and humans displays
287 intact or even enhanced sensitivity to the anorexigenic impact of oxytocin [16,120]. It has
288 been speculated that the relatively elevated cholesterol levels in obesity may boost high-
289 affinity binding of oxytocin to the OXTR [27,141]. Support for the assumption that oxytocin
290 signaling is altered in obesity comes from studies linking the OXTR gene to body weight
291 [142,143] and the observation that overweight subjects as well as newly diagnosed diabetic
292 patients display lower circulating concentrations of oxytocin when compared to normal-
293 weight controls [144]. Patients with Prader-Willi syndrome, who suffer from hyperphagic
294 obesity as a consequence of persistent food craving, display a 40% reduction in the number
295 and size of oxytocin neurons [145]. Pilot experiments in patients with this syndrome who
296 received oxytocin substitution via the intranasal pathway for eight weeks yielded none of the
297 intended effects on body weight and psychosocial function, which might have been due to a
298 lack of feed-forward endogenous oxytocin release after exogenous delivery [146]. In related
299 studies [147], young children with Prader-Willi syndrome improved their social and food-
300 related behavior after a four-week oxytocin intervention. Taken together, these findings

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

307 In animal experiments, DIO rhesus monkeys receiving subcutaneous oxytocin for four
308 weeks reduced their food intake by around 27% and their body weight by 3.3%, while their
309 energy expenditure increased by 14% [9]. Obese human subjects reduced their food intake by
310 around 10% in the first hours after acute intranasal administration [16]. When obese
311 individuals received four daily intranasal doses of 24 IU oxytocin for a duration of eight
312 weeks, they were observed to lose around 9 kg of body weight and to show a decrease in
313 waist and hip circumference [103]. Since the interpretation of these results is complicated by
314 the large pre-administration differences in BMI and age between the treatment and the
315 control groups (36 vs. 30 kg/m², 29 vs. 41 years), further and possibly larger trials are clearly
316 needed to sound the potential of oxytocin as an anti-obesity drug. In these studies it will be of
317 high relevance to address potential sex differences, which are suggested by some experiments
318 in animals [13], and carefully control for side effects on metabolic parameters but also
319 psychosocial functions. Although the intranasal administration of oxytocin at doses from 18-
320 40 IU – the range that comprises most doses commonly applied in experimental settings –
321 does not acutely induce distinguishable side-effects according to meta-analyses [47] chronic
322 oxytocin administration was associated with detrimental effects on social behavior in a
323 number of animal studies [151–153]. While it is unclear whether these findings can be
324 directly translated to the human situation, they pose a certain caveat to respective clinical
325 trials [154].

326

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

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

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

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