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The effects of oxytocin on eating behaviour and metabolism in humans

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Oxytocin, a hypothalamic hormone that is secreted directly into the brain and enters the peripheral circulation through the posterior pituitary gland, regulates a range of physiologic processes, including eating behaviour and metabolism. In rodents and nonhuman primates, chronic oxytocin administration leads to sustained weight reduction by reducing food intake, increasing energy expenditure and inducing lipolysis. Oxytocin might improve glucose homeostasis, independently of its effects on weight. Clinical studies are beginning to translate these important preclinical findings to humans. This Review describes key data linking oxytocin to eating behaviours and metabolism in humans. For example, a single intranasal dose of oxytocin can reduce caloric intake, increase fat oxidation and improve insulin sensitivity in men. Furthermore, a pilot study of 8 weeks of oxytocin treatment in adults with obesity or overweight led to substantial weight loss. Together, these data support further investigation of interventions that target pathways involving oxytocin as potential therapeutics in metabolic disorders, including obesity and diabetes mellitus. Therapeutic considerations and areas for further research are also discussed.

Oxytocin is a nine amino acid peptide hormone that binds to the oxytocin receptor, which is a member of the G-protein coupled receptor family, to regulate a range of physiologic processes, including eating behaviour and metabolism. Produced in the supraoptic nucleus and paraventricular nucleus (PVN) of the hypothalamus, oxytocin is released to brain regions involved in energy metabolism via dendritic diffusion (for example, the ventromedial nucleus (VMH)[1,2]), as well as axonal connections of parvocellular oxytocin neurons to other regions, including the arcuate nucleus (ARC) [3], ventral tegmental area (VTA)[4], nucleus accumbens [5], nucleus tractus solitarius (NTS) [6,7] and spinal cord [7,8]. There are also axonal connections of magnocellular oxytocin neurons to the posterior pituitary gland, which secretes oxytocin to the peripheral circulation. In addition, oxytocin is produced and released in local tissues, such as the gastrointestinal tract [9], where oxytocin has autocrine and paracrine effects via oxytocin receptors[10,11].

Although endogenous oxytocin does not readily cross the blood–brain barrier, behavioural studies indicate that circulating oxytocin might directly enter the hindbrain or act on the vagus nerve [12-15], and a study in nonhuman primates indicates that oxytocin at supraphysiologic concentrations administered intravenously or intranasally enters the

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cerebrospinal fluid (CSF) [16]. Furthermore, exogenous oxytocin administration might promote endogenous oxytocin secretion either directly through PVN oxytocin autoreceptors or indirectly through peripheral oxytocin receptors [17,18]. The oxytocin receptor is widely distributed in the central nervous system (for example, the hypothalamus, basal ganglia, VTA, nucleus accumbens, frontal cortex, insula, NTS and spinal cord) and peripheral regions that are key for the control of food intake and metabolism (for example, vagus nerve, anterior pituitary gland, adipocytes, gastrointestinal tract and pancreas) [8,10,11,19-30,8,31].

Animal studies indicate that oxytocin is a potent regulator of caloric intake and metabolism [8,14]. Oxytocin or oxytocin receptor knockout mice gain weight and develop late-onset obesity [32-34] and impaired glucose homeostasis [34]. In addition, mice with haploinsufficiency of single minded 1 (encoded by *Sim1*; mutations in *SIM1* are associated with hyperphagic obesity in humans) have low levels of oxytocin mRNA in the hypothalamus, and oxytocin administration reverses their excessive food intake and weight gain [35]. Exogenous oxytocin administration in mice, rats and monkeys, whether given centrally or peripherally, leads to sustained weight suppression by reducing food intake, increasing or maintaining energy expenditure, and promoting lipolysis [8,14,18,36-38]. Independent of effects on weight, oxytocin administration can improve glucose homeostasis in diet-induced obese or diabetic rodents [18,36]. These findings in animals indicate that pathways involving oxytocin might provide novel therapeutic targets for obesity and metabolic disorders. Clinical investigations are beginning to translate these important findings to humans.

Measurement of oxytocin in samples

In interpreting human data, it is important to recognize that measurement of oxytocin levels in blood samples is controversial and rigorous validations of assays have not been performed [39,40]. Older radioimmunoassays yielded results comparable to bio-assays and typically reported oxytocin levels after extraction of <10 pg/ml in healthy young men and non-pregnant or lactating women, with levels up to 24 pg/ml during lactation and 114 pg/ml during labour[39].

Unfortunately, using newer commercially available radioimmunoassays, oxytocin levels can be falsely elevated due to interference of other substances [41]. In the past decade, most publications reporting oxytocin in serum or plasma samples use commercially available enzyme immunoassays (ELISA), which yield levels that are up to two orders of magnitude higher than traditional radioimmunoassays when extraction is not performed[39]. Extraction before the ELISA filters out some, but not all, of the interfering substances and yields overall levels of similar magnitude to the traditional radioimmunoassays [41]. The ELISA might detect oxytocin fragments or degradation products, and the biological activity of these molecules is unknown [41]. In a paper published in 2016, it was posited that extraction might result in falsely low oxytocin levels due to elimination of protein-bound oxytocin[42]. In sum, studies reporting oxytocin levels using immunoassays are measuring oxytocin immunoreactive products, not absolute values of oxytocin, and levels cannot be compared between studies. However, these assays might be useful for the comparison of relative levels of peripheral oxytocin between groups and investigating the relationship between oxytocin levels and relevant clinical endpoints.

Newer techniques free oxytocin from protein binding by reduction–alkylation reactions, followed by liquid chromatography-mass spectrometry (LC-MS)[42]. After interfering substances are removed by solid phase extraction, the samples undergo high-performance liquid chromatography separation and measurement by mass spectrometry, which is highly selective and sensitive. The addition of a stable isotope of oxytocin (5x deuterated oxytocin) as the first step during LC-MS analysis enables accurate corrections for any loss of analytes or gain in signal strength due to concentration. Using this methodology, oxytocin levels in the ng/ml range (which is ≥1,000 times the levels reported using traditional techniques) have been reported[42]. These data suggest that much of oxytocin is protein-bound and not measured using traditional approaches. The biological relevance of protein-bound versus free oxytocin is an important question to be investigated.

Several other caveats need to be considered when interpreting data on oxytocin levels. Firstly, central and peripheral oxytocin secretion might be coordinated or independent of one another, and therefore peripheral levels might not reflect central functioning [43-46]. Secondly, CSF levels of oxytocin might not mirror activity in specific brain circuits. Thirdly, blood levels of oxytocin might not reflect local autocrine and/or paracrine oxytocin activity. Finally, the measurement of oxytocin in other biological samples (for example, urine and saliva) is not well-validated and the biological importance of these data is not yet clear[39].

Oxytocin dose

Oxytocin is typically given intravenously at doses of 1-30 mIU/min during labour and 10 IU post-partum to prevent haemorrhage (1 mg oxytocin is equivalent to 600 IU (WHO International Standard); therefore a dose of 1 mIU/min is approximately 1.7 ng/min). Metabolic studies in humans have often used doses that are higher than the 1 mIU/min required for inducing contractions in pregnancy and the estimated 14 IU oxytocin contained in the human posterior pituitary gland [47]. Doses used in these studies are therefore supraphysiologic, even when accounting for differences in routes of administration [48]. Evidence indicates that oxytocin at a supraphysiologic dose (80 IU) delivered either intranasally or intravenously crosses the blood brain barrier [16] and therefore might have direct central effects, in addition to peripheral effects. Some of the effects seen at supraphysiologic doses might be due to oxytocin acting at vasopressin receptors [49]. Studies are needed to clarify the relative contributions of these receptors in mediating the effects of exogenous oxytocin.

Eating behaviour

Experiments in rodents, nonhuman primates and humans consistently show that oxytocin reduces caloric consumption [14,18,35,50-52]. These effects are almost immediate and in animal models are sustained with repeated dosing [14,18,37,38,50,51]. With the exception of one study demonstrating that oxytocin reduces food intake and weight gain in female *Sim1* haploinsufficent mice [35], most studies have included only males, leaving the question of whether oxytocin also reduces food intake in females unclear. Interestingly, obese rodents seem to be more sensitive to oxytocin treatment than their lean counterparts [38]. Preclinical studies have demonstrated a preferential effect of oxytocin in reducing carbohydrate

consumption [14,53-56]. Although some rodent studies have not found that oxytocin effects intake of lipid emulsions [54,55], others have demonstrated that oxytocin suppresses consumption of high-fat diets [17,18,37,38]. Preclinical studies implicate both central (homeostatic, for example, VMH and ARC [1,3], and hedonic (for example, VTA and nucleus accumbens) [4,5], autonomic (NTS and dorsal motor nucleus of vagus) [6,7] and peripheral (gastrointestinal system and vagus nerve) [37,57-60] signalling pathways in the modulation of food intake. Furthermore, oxytocin might affect appetite indirectly by altering levels of other appetite-regulating hormones (for example, increased levels of the anorexigenic hormones CCK and GLP1) [57,61,62].

Evidence increasingly suggests that in humans, oxytocin is involved in normal and aberrant eating behaviours. In anorexia nervosa, an eating disorder characterized by severe chronic food restriction despite self-starvation and markedly low weight, low CSF levels of oxytocin were found in five women with low-weight restrictive [63] (but not low-weight [63] or weight restored binge-purge[64] subtypes) anorexia nervosa compared with controls. In addition, peripheral levels of oxytocin in response to stimulation were suppressed in seven low-weight women with anorexia nervosa; levels normalized with weight restoration [65]. Low basal serum levels of oxytocin have also been reported in acute (low-weight) and partially-recovered (normal weight) women with anorexia nervosa [66-68]. Furthermore, post-prandial oxytocin levels have been linked to the severity of eating disorder psychopathology and functional magnetic resonance imaging (fMRI) hypoactivation of food motivation neural circuitry in low-weight and weight-restored women with anorexia nervosa, which suggests that oxytocin might have a role in the aetiology of anorexia nervosa[69]. By contrast, several studies have not demonstrated differences in CSF levels of oxytocin between women with active [63] or recovered [64] bulimia nervosa and healthy individuals. Furthermore, no differences were found in basal or stimulated peripheral levels of oxytocin in women with bulimia nervosa compared with controls[65,68]. In the past 5 years, studies in women have identified associations between genetic variation in the oxytocin receptor and eating disorder diagnosis (bulimia nervosa) [70], eating disorder thoughts and behaviours (in those with anorexia nervosa as well as a community sample of women) [71-73], food preoccupation (in anorexia nervosa) [71] and reported nutrient intake (in a community sample of women) [72].

A single-dose randomized placebo-controlled crossover study of 40 IU intranasal administration of oxytocin in women showed that oxytocin reduced self-reported food intake in the subsequent 24 h in women with bulimia nervosa, but not in women with anorexia nervosa or healthy controls [74]; however, a test meal was not performed. In a study of intranasal administration of oxytocin (12-24 IU twice a day) in boys and girls with Prader–Willi syndrome (a genetic syndrome characterized by severe early onset obesity and hyperphagia), 4 weeks of oxytocin treatment reduced the incidence of abnormal food-related behaviours (for instance, preoccupation with food) in a subset of younger children (those aged 6-10 years), but not in those 11-14 years old[75]. Oxytocin did not affect food intake at a test meal in these children; however, the ability to detect a difference was hindered by the fairly small size of the meal, which was finished in its entirety by nearly all participants, who had hyperphagia[75].

To date, three human studies – all exclusively in men – that investigated the effects of intranasal administration of oxytocin on food intake in individuals without eating disorders have been published [51,52,76]. In a randomized, placebo-controlled cross-over study of a single intranasal dose of 24 IU oxytocin in 25 healthy men without diabetes mellitus (13 normal-weight and 12 with overweight or obesity), oxytocin reduced caloric intake at a breakfast test meal by 122 kcal with a preferential effect on fat consumption; intake of fat was significantly reduced, while intake of carbohydrates and protein was not significantly reduced [51]. Although initial work using the same intranasal dose of oxytocin in normal-weight men did not show suppression of caloric intake at a breakfast buffet [52], a follow up study demonstrated a reduction of 147 kcal in men with obesity[76], which is consistent with the animal data that suggests that obesity might be a particularly oxytocin-sensitive state [38]. The authors found that oxytocin reduced consumption of a post-prandial snack, particularly chocolate cookies, to a similar extent in men who were normal-weight or had obesity[76].

Each of the three human studies[63,64,90] assessed for changes in appetite using visual analogue scales and found no evidence that oxytocin effected participants' self-report of fasting or post-prandial appetite, which demonstrates that oxytocin might alter eating behaviour without the awareness of the individual. This finding is consistent with reports from smaller studies showing no effects of intravenous administration of oxytocin on subjective satiety in healthy individuals [77] or in patients with diabetic gastroparesis or functional dyspepsia [78], but is in contrast to one study that reported reduced satiety in healthy individuals [79]. Furthermore, several small studies using intravenous infusions of oxytocin (20-80 mIU/min) in men and women who were healthy [79] or had functional dyspepsia [78] found that oxytocin had no effect on the volume of liquid meal intake required to induce satiety. These data highlight the importance of obtaining objective measures, such as food intake, at a test meal and/or brain imaging in this line of research.

The relationship between postprandial serum levels of oxytocin and hypoactivation detected with fMRI of the hypothalamus – a brain region critical to homeostatic regulation of food consumption – as well as hypoactivation of areas responsible for reward-driven eating, such as the orbitofrontal cortex, in response to visual food stimuli in women with anorexia nervosa [69] supports preclinical evidence of oxytocin's role in both homeostatic and hedonic food motivation [8]. In addition, the preferential effects of intranasal administration of oxytocin in reducing consumption of more palatable foods, such as fats and carbohydrates, by men [51,52,76] is consistent with the concept that oxytocin might inhibit food intake in part by modulating reward-related food motivation and/or impulse control neurocircuitry. This concept is in line with a study published in 2016 showing that a single intranasal dose of 24 IU oxytocin increased activation of brain circuitry involved in cognitive control (detected using fMRI) and, at the trend level, reduced food craving when women were asked to cognitively control the urge to eat while viewing images of palatable foods [80]. This finding is also consistent with animal studies demonstrating that administration of oxytocin to the VTA[56] or nucleus accumbens[81], which are regions of the brain involved in reward that receive oxytocin projections from the PVN[4] and express oxytocin receptors[23-25], inhibits sucrose intake. Further research examining the specific effects of oxytocin on caloric intake and underlying mechanisms in humans will be important (Figure 1).

Peripheral sites of oxytocin action have also been implicated as potential modulators of appetitive behaviours. Studies in rats suggest that oxytocin might induce satiety in part by slowing gastric emptying [57-60]. The data in humans, however, are inconsistent with one study in patients with diabetic gastroparesis reporting prolonged gastric emptying time (40-80 mIU/min) [78], and studies in healthy individuals showing no effects (40 mIU/min)[77], or accelerated gastric emptying (0.33 IU/min) [82] following intravenous administration of oxytocin. Although a study in healthy men and women found that the oxytocin antagonist atosiban increased gastric emptying time [77], the authors speculate that these effects could have been due to actions at the vasopressin receptor. These conflicting results might reflect differences in the populations studied and/or small sample sizes. Two studies have examined the effects of oxytocin on the colon in humans. In women, intravenous administration of oxytocin (20 mIU/min or 40 mIU/min) increased colonic motility in response to a lipid infusion by feeding tube [83]. In a study of 26 patients with irritable bowel syndrome and constipation, intravenous administration of oxytocin at doses of 20-50 mIU/min reduced their perception of colonic distention [84]. The clinical significance of these findings is unclear and further studies are needed to determine dose and population-specific effects of oxytocin on gastroenterological function and appetitive behaviours.

Several studies in humans have examined the effects of oxytocin on other appetite-regulating hormones. While intravenous administration of oxytocin reduces the typical lipopolysaccharide-induced increase in levels of ghrelin (which is orexigenic) [85], 24 IU intranasal administration of oxytocin did not result in statistically significant changes in fasting or post-prandial levels of ghrelin [51,52]. Oxytocin increased CCK levels, but this change was not related to differences in caloric consumption between oxytocin and placebo conditions [51]. Oxytocin had no statistically significant effects on the levels of anorexigenic hormones leptin, GLP1 or PYY [51,52]. Reduced levels of cortisol, which have been previously demonstrated in animal and human studies, were associated with reduced consumption of chocolate cookies in normal weight (but not obese) men receiving oxytocin [52,76]. In future studies, it will be important to examine the effects of oxytocin on other appetite-regulating hormones and whether some of the effects of oxytocin on caloric intake could be mediated by other hormones.

Lipid metabolism and body fat

Preclinical studies indicate that oxytocin induces lipolysis [14,18] and fat oxidation [18,37,86], which in turn, independent of food intake, lead to reduced body fat and weight [18]. Notably, oxytocin reduces visceral and liver fat [37], which are metabolically important fat depots that are associated with an increased risk of the metabolic syndrome and cardiovascular disease [87].

In men and women, endogenous peripheral levels of oxytocin are high in those with obesity [88,89] and oxytocin levels in different populations across the weight spectrum are correlated with BMI and levels of body fat [66,89-91]. A notable exception is a study showing low levels of oxytocin in adults with obesity compared with adults of a normal weight; thus, oxytocin levels were negatively associated with BMI. However, these results might have been confounded by the fact that a large proportion of participants had type 2 diabetes mellitus, a

condition associated with low oxytocin levels[92]. Published in 2016, results from the MINOS study of men aged 50-85 yrs demonstrated higher endogenous levels of oxytocin in men with the metabolic syndrome compared to those without metabolic syndrome. Furthermore, higher oxytocin levels were associated with greater odds of metabolic syndrome after adjusting for confounders including leptin levels. [91]. High oxytocin levels were associated with increased central fat and waist circumference, which are surrogate markers for visceral fat [91].

In the 1960s, an experiment in women showed that intravenous administration of oxytocin (10 mIU/kg) increased plasma levels of nonesterified free fatty acids and reduced plasma levels of triglycerides[93], which is consistent with the lipolytic effect of oxytocin that has been demonstrated in animal models [14,18]. Several human studies published in the past 5 years have used intranasal oxytocin as a physiologic probe to study the effects of oxytocin on lipid metabolism and body fat [36,51]. A single dose of intranasal oxytocin (24 IU) in men resulted in a drop in respiratory quotient as assessed by indirect calorimetry 30 min after oxytocin administration, which is consistent with an increase in fat oxidation [51]. In a small study of 8 weeks of sustained intranasal administration of oxytocin (24 IU before meals and at bedtime) in men and women who were overweight or had obesity, oxytocin led to weight loss with an improved lipid profile (lower levels of total cholesterol and LDL cholesterol) and reduced waist circumference [36]. Imaging was not performed to assess for changes in total body fat or specific fat depots [36]. The study authors noted that oxytocin resulted in slightly improved results from liver function tests, which could reflect reduced hepatic steatosis [36]. Further studies are warranted to examine the effects of oxytocin on lipid metabolism and body fat depots.

Energy expenditure

A major barrier to maintenance of weight loss in humans is the physiologic reduction in energy expenditure that occurs with reduced food intake and weight [94]. Unlike existing pharmacological options, which primarily target food consumption or absorption, oxytocin not only reduces food intake but, in diet induced obese rodent and nonhuman primate models, also promotes energy expenditure, which enables maintenance of weight reduction [14,18,38,86]. How oxytocin increases energy expenditure is not yet clear; however, some preclinical evidence suggests that oxytocin may lead to preferential preservation of lean body mass, a key determinant of energy expenditure, despite weight loss [86]; activation of brown fat [32-34]; and/or the conversion of white adipose tissue to beige fat that is capable of thermogenesis [90,95].

In young female athletes and non-athletes aged 14-21 yrs, fasting levels of oxytocin were positively associated with resting energy expenditure, providing the first evidence for such a link in humans [90]. However, studies of a single intranasal dose of oxytocin (24 IU) in men of a normal weight, or who had overweight or obesity found no acute effect of oxytocin on resting or post-prandial energy expenditure measured by indirect calorimetry [51,52]. It is possible that chronic oxytocin exposure is required to induce changes in energy expenditure, and therefore effects on energy expenditure were not captured in these single dose

experiments. Whether sustained oxytocin will increase energy expenditure in humans as it does in animal models will be an important area of investigation.

Body weight

Oxytocin is emerging as a promising novel weight-loss therapy for obesity, as evidenced by review articles published on this topic over the past several years [8,96,97] and current clinical research studies registered on ClinicalTrials.gov (NCT 02849743, 03043053, 03119610). Experiments in rodents and nonhuman primates demonstrate that chronic peripheral or central administration of oxytocin results in sustained weight loss attributed to reduced food intake, maintenance of energy expenditure despite weight loss and increased lipolysis [14,18,37,38,86].

Human studies have shown that peripheral levels of oxytocin are low in patients with anorexia nervosa [66,68], high in those with obesity [88,89] and positively associated with BMI and fat mass [66,89]. Furthermore, oxytocin levels drop with weight loss following gastric banding [88]. Together, these preclinical and clinical data suggest that oxytocin could act as a signal of energy availability: high oxytocin levels (for example, in obesity) appropriately signal the need to reduce caloric intake and increase energy expenditure.

Dysfunctional oxytocin signalling might contribute to weight gain in human genetic syndromes of severe obesity. In a genome-wide association study of white children in the UK, copy number variation in genes that encode proteins in the oxytocin receptor pathway were associated with severe early onset obesity [98]. Furthermore, hypothalamic oxytocin deficiency has been implicated in the pathogenesis of Prader–Willi syndrome[99,100]. In these patients, fairly low levels of oxytocin have been reported in the CSF [99], and post-mortem studies have identified a reduced number of oxytocin-expressing neurons in the PVN of the hypothalamus [100]. In addition, polymorphisms of the oxytocin receptor (A-allele of rs53576) are associated with increased risk of obesity in children of low socioeconomic status[101].

To date, only one study has examined whether oxytocin administration reduces body weight in humans who have overweight or obesity but are otherwise healthy. This randomized, placebo-controlled study of 24 IU oxytocin delivered intranasally four times per day in men and women who were overweight or had obesity demonstrated that oxytocin led to substantial weight loss over 8 weeks [36]. This study was limited by a small sample size (9 participants randomly assigned to receive oxytocin) and the groups were not well-matched for age or baseline weight. However, the body weight loss of approximately 9 kg (or 9%) with oxytocin was similar to the weight loss seen with the most effective FDA-approved medications for obesity [102,103].

In contrast to the previous study [36], two randomized, placebo-controlled cross-over studies of intranasal administration of oxytocin (12-40 IU twice daily) in children and adults with Prader–Willi syndrome did not result in statistically significant weight loss [75,104]. Several potential explanations for the failure of oxytocin to reduce weight in these studies exist. Firstly, the lower daily dose and frequency of oxytocin administration than in the previous study. Secondly, Prader-Willi syndrome is associated with structural abnormalities of the

PVN, including reduced number of oxytocin neurons [100]; it is therefore plausible that these patients may not be able to respond to exogenous oxytocin (for example, there may be a reduced number of hypothalamic oxytocin receptors and/or an inability to respond to oxytocin stimulation with endogenous oxytocin release).[104] Thirdly, children might have a different response to oxytocin compared with adults. Fourthly, in one of the studies, weight was not a primary endpoint [75].

Glucose homeostasis

Oxytocin receptors are present on α cells and β cells in pancreatic islets [29]. Furthermore, oxytocin administered at physiologic concentrations increases insulin release in the isolated rat pancreas [105]. Studies examining the effects of oxytocin on glucose homeostasis have yielded conflicting results and are very much dependent on the experimental model used. While some studies of central or peripheral administration of oxytocin in animal models (for example, in lean rats or obese diabetic ob/ob mice) have shown that oxytocin induces hyperglycaemia [26,106], others (for example, in lean or diet-induced obese mice, diet-induced obese rats, obese diabetic db/db mice, or streptozotocin-induced diabetic mice with impaired beta-cell function) have clearly demonstrated the therapeutic potential of using oxytocin or oxytocin analogues to increase insulin secretion, insulin sensitivity and glucose tolerance independent of effects on weight or food intake [8,17,18,36,37,95,107,108].

Human studies show inconsistent effects of oxytocin on glucose homeostasis, which might reflect differences in route of administration (for instance, intravenous versus intranasal and bolus versus continuous infusion), dose and/or populations studied. Acute effects of oxytocin on glucose homeostasis in humans were first demonstrated using intravenous administration of oxytocin more than 50 years ago. The study demonstrated that an intravenous bolus of oxytocin (10 mIU/kg) in postpartum women or women who were not pregnant or postpartum resulted in a dramatic lowering of blood levels of glucose over the 3 h experiment [93]. By contrast, another study of postpartum women found no effect of an intravenous dose of oxytocin (10 IU) on glucose or insulin levels [109]. This discrepancy may have been due to differences in dose, which was more than ten times higher in the second experiment. In a small study of men, 6 IU (an initial dose of 2 IU plus an infusion of 4 IU over 1 h), but not 3 IU (an initial dose of 1 IU plus an infusion of 2 IU over 1 h) oxytocin intravenously increased insulin levels in response to intravenous administration of glucose (0.33 g/kg) without affecting glucose levels or the glucagon, growth hormone or cortisol responses [110]. Another study reported that continuous intravenous infusion of oxytocin (0.2 IU/min over 60 min) resulted in hyperglycaemia, accompanied by increased release of glucagon, insulin and adrenaline and reduced release of cortisol in healthy, young men aged 21-26 yrs [111]. Furthermore, in response to insulin-induced hypoglycaemia, oxytocin infused intravenously at this dose attenuated the drop in levels of glucose, increased levels of glucagon and adrenaline and reduced cortisol levels [111,112]. Using a euglyceamic euinsulinaemic clamp, it was also shown that the same dose of intravenous oxytocin increased hepatic glucose output in healthy young men aged 22-28 yrs [113].

Studies published in the past few years that used intranasal administration of oxytocin in men without diabetes mellitus have reported consistently beneficial effects on glucose

homeostasis [51,52,76,114]. In healthy men without diabetes mellitus who had a normal weight, were overweight or had obesity, 24 IU oxytocin intranasally – the same dose that is under investigation for weight loss in obese adults [36](ClinTrials.gov, NCT03043053) – reduced fasting levels of insulin while maintaining normal levels of glucose, which resulted in improved insulin sensitivity [51]. In the fed state, 24 IU oxytocin intranasally in separate groups of healthy normal-weight men and men with overweight or obesity reduced glucose levels without a change in insulin or C-peptide levels, independent of caloric intake [52,76]. In response to a 75 g oral glucose tolerance test, 24 IU oxytocin intranasally blunted the rise in levels of glucose and resulted in a more rapid, but attenuated insulin and C-peptide peak in 29 normal-weight healthy men [114]. The authors found that oxytocin improved β-cell responsivity to the glucose challenge [114]. However, a pilot study of intranasal administration of oxytocin (24 IU before meals and bedtime) for 8 weeks in a small group of men and women without diabetes mellitus who had overweight or obesity did not show statistically significant changes in fasting or postprandial levels of glucose or insulin despite weight loss [36].

Men and women with type 2 diabetes mellitus [92] and women with type 1 diabetes mellitus [115] have been shown to have lower levels of oxytocin than controls. Furthermore, in those with type 2 diabetes mellitus, low fasting levels of oxytocin were associated with higher levels of glucose and insulin, both after fasting and after an oral glucose tolerance test, as well as higher HOMA-IR results and levels of HbA_{1c} [92]; these findings suggest that diabetes mellitus could be a state of oxytocin deficiency. However, an experiment administering continuous intravenous infusion of oxytocin (0.2 IU/min) to patients with type 1 diabetes mellitus resulted in hyperglycaemia [112], which is similar to findings with this dose and route of administration in healthy young men [111].

In summary, studies examining acute effects of intravenous oxytocin on glucose homeostasis in humans have shown mixed results with low dose (10 mIU/kg, i.e. ≤1 IU) oxytocin reducing glucose levels and higher dose oxytocin showing no effect (3-10 IU) or increasing (12 IU) glucose levels. While a number of studies of single dose intranasal oxytocin (24 IU) in non-diabetic men have resulted in improved glucose homeostasis, an eight week study of short-term intranasal oxytocin (24 IU four times per day) did not yield improvement in glucose parameters despite achieving weight loss. Further research examining dose-dependent effects of different routes of oxytocin administration, taking sex and physiologic context into account, is warranted. Studies in patients with prediabetes mellitus and diabetes mellitus will be particularly important.

Downregulation of the HPA axis

In addition to having direct beneficial metabolic actions, oxytocin might contribute additional complementary metabolic effects by downregulating activation of the hypothalamic–pituitary–adrenal (HPA) axis. The negative effects of cortisol on metabolism, including effects on lipid metabolism, body fat deposition and glucose homeostasis, are well-established [116]. Oxytocin receptors are located in the anterior pituitary and adrenal glands [30,117], and intravenous or intranasal administration of oxytocin in humans reduces levels of adrenocorticotropic hormone and cortisol under basal and stress conditions [118-122].

Intravenous administration of oxytocin completely blocked adrenocorticotropic hormone stimulation in response to corticotropin-releasing hormone in normal-weight men [123]. Although oxytocin reduces cortisol levels, hypoadrenalism is not a reported adverse effect of this drug at therapeutic doses. Further research is needed to determine whether the effects of oxytocin on the HPA axis lead to an improved metabolic profile.

Therapeutic potential

Oxytocin and interventions targeting related pathways to increase the actions of the oxytocin signal are promising agents in the treatment of obesity and metabolic disorders, including diabetes mellitus (Figure 2). However, some important points must be considered when developing oxytocin therapeutics, including its short half-life[31] and the current limitations in our knowledge about mechanisms and actions of oxytocin, as well as the safety of chronic administration in humans.

Synthetic oxytocin is FDA-approved and widely used for induction of labour and control of postpartum uterine bleeding, and is readily available in intravenous and intramuscular formulations [124]. Given the short half-life of oxytocin (on the order of 2-8 minutes in peripheral blood [125,126] and 19-28 minutes in CSF [127])[128], intramuscular or intravenous bolus administration would not be feasible for chronic administration. Although not currently approved by the FDA, intranasal formulations of oxytocin are commercially available outside the USA (for instance, in Europe) to facilitate milk letdown in nursing mothers, and has been used in human investigations [129]. However, the intranasal formulation is inconvenient (it consists of 24 IU or six sprays of 4 IU given four times per day) and results in imprecise dosing. Oxytocin is a pulsatile hormone [130-133] and the implications of basal (or continuous) versus pulsatile (or bolus) oxytocin exposure is not yet clear. Furthermore, the effect of oxytocin feed-forward regulation (that is, stimulation of oxytocin release by oxytocin) in extending effects of exogenously administered oxytocin is not well-defined. In diet-induced obese mice, continuous subcutaneous administration of oxytocin using a minipump is more than three times more effective in achieving weight reduction than a single daily injection of the same dose (13.0% vs. 3.6%) [37], which suggests that longer acting oxytocin formulations would have greater efficacy than current options. Longer-acting oxytocin analogues, such as carbetocin, [Ser4,Ile8]-oxytocin and [Asu1,6]-oxytocin have been developed, and improve metabolic parameters (such as weight loss and glucose homeostasis) in obese diabetic mice [26,36]. Improving our currently limited mechanistic understanding of how oxytocin works in humans will be a critical step in bringing oxytocin therapeutics into the clinic. Elucidating the full range of on and off target effects in order to optimize efficacy and minimize tolerability and safety concerns will also be important. Many unanswered questions exist, including whether and how central and/or peripheral oxytocin mediates its metabolic effects. Optimal dosing will also need to be established. Pharmacokinetic studies are limited by challenges in accurately measuring oxytocin levels [39]. Newer LC-MS methods may be useful in overcoming these limitations.

Although oxytocin is often administered to women around the time of childbirth, chronic use of oxytocin is not well studied and its safety for metabolic indications has not yet been established. A direct comparison of doses is difficult because oxytocin is given intravenously

as a continuous infusion to induce labor, whereas single doses of intranasal oxytocin (four times per day) are under investigation for weight loss. However, the dose of intranasal oxytocin that reduces food intake, increases the use of fat as a fuel for the body, and improves glucose homeostasis in men (24 IU) [51,52,76,114] falls within the range of total intranasal oxytocin used in a series of patients receiving this for the induction and maintenance of labor in 1968-1970, when intranasal oxytocin was used clinically as an alternative to intravenous oxytocin [134]. In one series, the mean total dose of oxytocin used for induction or stimulation of labor was 99 IU [135], similar to the daily dose that is under study for obesity (96 IU) [36](ClinTrials.gov, NCT03043053). Based primarily on our current knowledge of possible adverse effects in labour and delivery with oxytocin, key safety issues that will need to be assessed with chronic use for metabolic disease include cardiovascular risk including arrhythmias and changes in blood pressure, as well as hyponatraemia [124]. Less concerning adverse effects that could limit tolerability include headache or nausea [124]. Oxytocin for metabolic indications would be contraindicated in pregnancy given the risk of uterine contractions. Investigations of chronic intranasal administration of oxytocin in humans have extended up to 6 months with no serious safety concerns reported [36,75,104,129,136-139]. Although oxytocin is under investigation as a potential therapy for neuropsychiatric disorders, such as autism spectrum disorders, in children [138], the long-term consequences of oxytocin administration in development are unknown and warrant investigation. Further study of chronic oxytocin use will be important, particularly in patients with obesity and its associated comorbidities, to demonstrate safety in this population.

Alternative ways to increase oxytocin signalling, for instance, by promoting oxytocin secretion, increasing oxytocin receptor activity or inhibiting oxytocin degradation, should also be explored.

Conclusions

Translational human studies are beginning to define the effects of oxytocin on eating behaviour and metabolism and support the therapeutic potential of oxytocin-based drugs for metabolic disorders, such as obesity and diabetes mellitus. Optimizing measurement techniques for biological samples is a critical step in improving our understanding of oxytocin physiology and translational applications. Further research examining dose-dependent effects and underlying mechanisms of oxytocin using different routes of administration (for example, intranasal versus intravenous and bolus versus continuous oxytocin exposure) and taking sex and physiologic context into account, will be important. The safety and tolerability of chronic oxytocin use in relevant clinical populations must also be established. Alternative ways to increase oxytocin signalling (for example, pharmacologic agents that increase secretion, act at the oxytocin receptor or inhibit oxytocin breakdown) should also be considered. Improving our mechanistic understanding of how and where oxytocin acts in humans will be critical to advancing clinical therapies.

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Biography

Elizabeth A. Lawson is Director, Interdisciplinary Oxytocin Research Program in the Neuroendocrine Unit at Massachusetts General Hospital (MGH) and Associate Professor of Medicine at Harvard Medical School. She is also a practicing neuroendocrinologist at the Neuroendocrine Clinical Center at MGH. Her research focuses on the effects of oxytocin on eating behaviour and metabolism in humans.

Box 1

Endogenous peripheral levels of oxytocin in humans

Positive associations

- Severity of eating disorder psychopathology and hypoactivation of food motivation brain regions on fMRI (post-prandial levels of oxytocin in anorexia nervosa)
- Body weight, BMI and body fat
- Resting energy expenditure

Negative associations

- Levels of glucose and insulin, HOMA-IR, HbA_{1c} levels (type 2 diabetes mellitus) during fasting and after an oral glucose tolerance test.

Box 2

Effects of intranasal administration of oxytocin in humans

Acute

- Reduces caloric intake at test meal and post-meal snack
- Reduces respiratory quotient, which is indicative of increased fat utilization
- Increases fasting and post-prandial insulin sensitivity; improves β-cell responsivity to oral glucose tolerance test
- Reduces hypothalamic–pituitary–adrenal activity and reactivity

Chronic

- Reduces body weight and waist circumference
- Reduces levels of total and LDL cholesterol

Key points

- Animal studies indicate that oxytocin is a potent regulator of caloric intake and metabolism; clinical investigations are beginning to translate these findings to humans.
- A single dose of intranasal oxytocin reduces caloric intake in men, particularly of more palatable foods, and these effects could be increased in men with obesity.
- Intranasal oxytocin acutely increases the use of fat as a fuel for the body, but effects of oxytocin in promoting energy expenditure have not been demonstrated in humans.
- An 8-week pilot study of intranasal oxytocin in a small group of men and women with overweight or obesity led to substantial weight loss.
- Independent of effects on body weight, oxytocin might improve glucose homeostasis, but data are conflicting.
- Pathways that involve oxytocin offer novel therapeutic targets for obesity and metabolic disease.

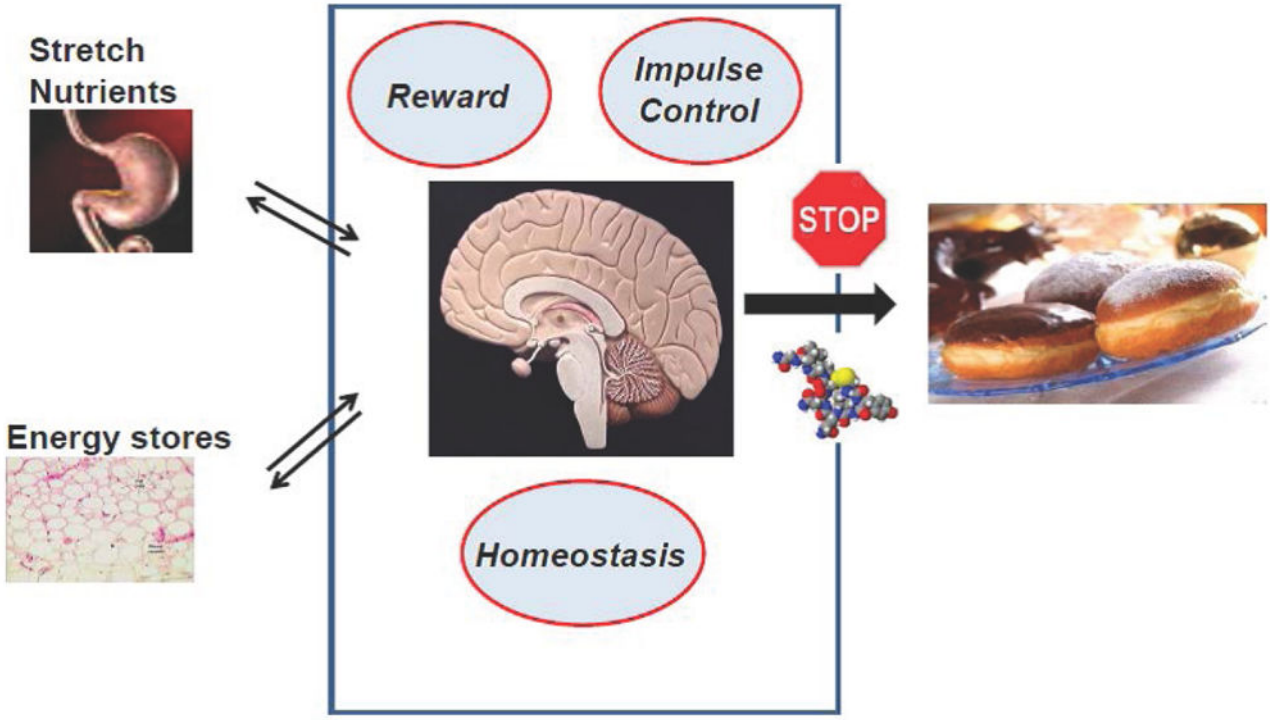

Figure 1. Hypothesized mechanisms underlying the effects of oxytocin on caloric intake

In response to peripheral signals that indicate energy availability, oxytocin acts on homeostatic, reward and impulse control brain circuitry to reduce caloric intake, particularly of more palatable foods.

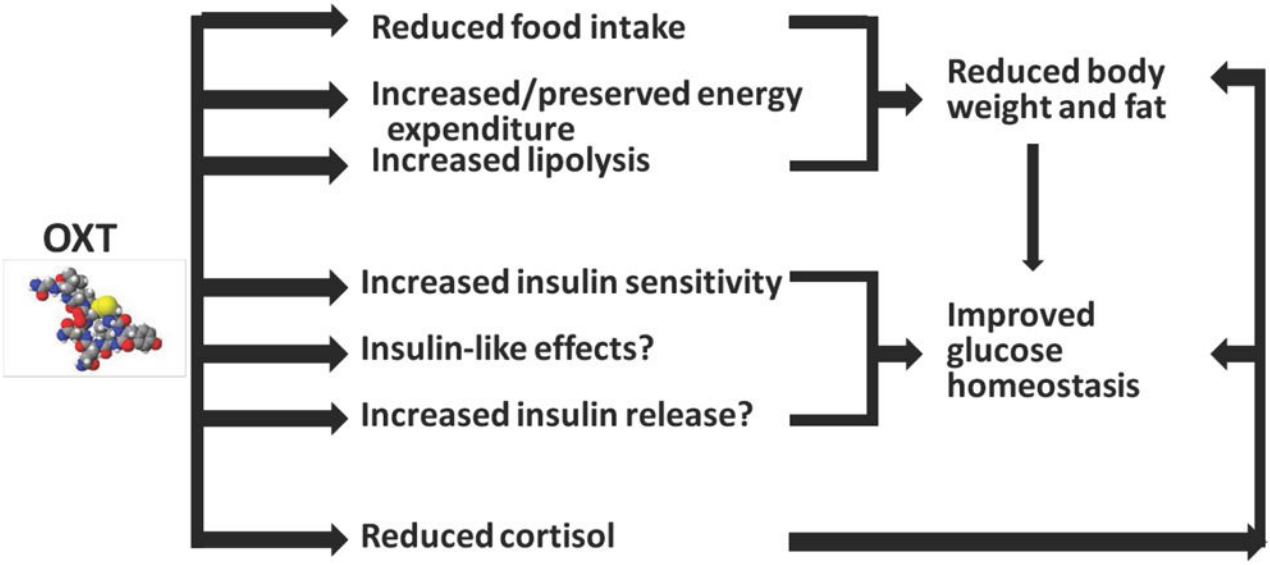

Figure 2. Proposed model of the effects of oxytocin on metabolic parameters

Oxytocin reduces body weight and fat and improves glucose homeostasis, highlighting its potential as a targeted therapy for metabolic disorders such as obesity and diabetes mellitus.