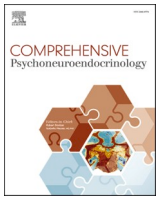
Comprehensive Psychoneuroendocrinology 19 (2024) 100242

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology



Understanding oxytocin in human physiology and pathophysiology: A path towards therapeutics

Elizabeth A. Lawson

Neuroendocrine Unit, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, 50 Staniford Street, Suite 750B, Boston, MA, 02114, USA

ARTICLE INFO

Keywords:
Oxytocin
Obesity
Eating behavior
Anorexia nervosa
Hypopituitarism
Oxytocin deficiency

1. Endocrine training and concept of multifaceted hormone impacting brain and metabolism

As a Fellow in Endocrinology at Massachusetts General Hospital (MGH) investigating endocrine complications of anorexia nervosa, I developed a fascination for hormones involved in metabolism that also act on the brain to modulate mental health and behavior. Oxytocin, a hypothalamic-pituitary hormone well known for inducing labor and lactation, sparked my interest given emerging evidence for broad physiologic and behavioral effects in both sexes. With funding from my incredibly supportive research mentor in the Neuroendocrine Unit, Anne Klibanski, I leveraged data and samples from my fellowship project (on the hypothalamic-pituitary-adrenal axis and bone health) to investigate oxytocin in anorexia nervosa, eventually leading to my first oxytocin publication and a clinical and translational research program focused on oxytocin in human health and disease.

2. Oxytocin deficiency in context of energy deficit

Anorexia nervosa, a psychiatric disorder characterized by food restriction despite severely low weight, is commonly accompanied by mental and physical comorbidities, including anxiety, depression, social-emotional functioning difficulties, and bone loss [1]. Studies in oxytocin and oxytocin receptor knockout animal models had shown that deficient oxytocin signaling was associated with weight gain [2,3], increased anxiety [4], depressive [5] and abnormal social behaviors [6], and osteoporosis [7]. There was also evidence that oxytocin or oxytocin agonist administration in rodents reduced food intake [8,9], reduced anxiety behaviors [4], promoted prosocial interactions [10], and improved bone mass [11]. Further, several small studies pointed to a possible oxytocin deficiency in females with anorexia nervosa. Compared to healthy controls, Demitrack et al. reported that five underweight women with restricting anorexia nervosa had low levels of cerebrospinal fluid oxytocin [12]. In seven women with anorexia nervosa, Chiodera et al. demonstrated an absent response of circulating oxytocin to known stimuli (insulin induced hypoglycemia; estradiol) that normalized with weight gain [13]. These findings suggested that in anorexia nervosa, oxytocin levels may be suppressed as a physiologic adaptation intended to increase caloric intake and conserve limited resources in the context of chronic starvation. Low oxytocin levels, in turn, might contribute to poor mental health and multifactorial bone loss [14]. However, circulating oxytocin levels in anorexia nervosa were not well established and the link between oxytocin and markers of energy homeostasis, bone health, and psychopathology in anorexia nervosa was unknown.

My fellowship project offered an opportunity to begin to probe the hypothesis that low oxytocin levels in the context of undernutrition contribute to comorbidities in anorexia nervosa [15], and to begin to clinically characterize oxytocin defiency in humans. In order to understand cortisol dynamics in anorexia nervosa, we had sampled blood every 20 min for 12 h overnight in women with anorexia nervosa and healthy controls and pooled each individual's samples to get an integrated measure of hormone exposure. We had leftover samples stored at −80°, and used these to measure overnight oxytocin levels in 17 women

E-mail address: ealawson@mgh.harvard.edu.

https://doi.org/10.1016/j.cpnec.2024.100242
Received 31 December 2023; Received in revised form 6 May 2024; Accepted 27 May 2024
Available online 28 May 2024

with anorexia nervosa and 19 healthy controls. I remember the excitement of analyzing these data and writing up my first oxytocin paper during a long weekend visit with family in the Catskill mountains, while my toddler was happily distracted by his great aunt and cousins. My research coordinator, Dan Donoho (now a pediatric pituitary surgeon), promptly emailed me relevant publications that I requested as I worked on the paper and Anne Klibanski immediately reviewed and provided feedback on my draft, demonstrating their enthusiasm for our findings and making it possible to complete the manuscript draft in record time. Consistent with my hypothesis, overnight oxytocin levels were low in women with anorexia nervosa, independent of estradiol levels, and positively associated with leptin (fat-derived marker of energy availability) and bone mineral density at the spine, such that those with the lowest leptin levels had the lowest oxytocin levels and the worst bone health [16].

In our initial manuscript submission, we had reported oxytocin results using an enzyme-linked immunosorbant assay (ELISA) without extraction, and reviewers rejected the paper, recommending that we use an extraction step. Pat Sluss, MGH Research Core Laboratory director and collaborator, ran our blood samples again using the same assay – this time with extraction – and found that while absolute levels of oxytocin were substantially lower after extraction, our findings were consistent (low oxytocin in anorexia nervosa positively correlated with leptin and bone mineral density). Our paper was (finally) published in the *Journal of Clinical Psychiatry* [16]. In later work, we published that extracted and unextracted oxytocin levels were highly correlated [17]. When using different assays (ELISAs; radioimmunoassay, RIA) and techniques (extracted versus unextracted), we have found oxytocin levels to be low in clinical populations [patients with energy deficit (females with anorexia nervosa (ELISA, extracted and unextracted) [16,18]; female athletes with oligoamenorrhea and decreased body fat (ELISA, unextracted) [17]; and men with pituitary disease and presumed oxytocin deficiency (arginine-vasopressin deficiency, formerly known as diabetes insipidus) (RIA, extracted) [19], and correlated with clinical endpoints (e.g., markers of energy availability (ELISA, extracted and unextracted) [16,18,20], bone health (ELISA, extracted and unextracted; RIA, extracted) [16–18,21], and mental health (ELISA, extracted and unextracted; RIA, extracted) [19,22–26]. Different assays and techniques provide markedly different absolute levels of oxytocin, likely reflecting loss of protein-bound oxytocin with extraction as well as measurement of oxytocin fragments (which may be biologically active) and heterophilic antibodies [27,28]. Absolute oxytocin levels using different assays and techniques cannot be compared. However, available oxytocin assays can be used to understand relative between-group differences in oxytocin signal, relationship to relevant endpoints, and response to intervention, providing important information regarding the oxytocin system in humans. Measurement of oxytocin is imperfect and developing and validating ways to detect different forms of oxytocin will be important.

To build on our work, I approached Madhusmita (Madhu) Misra, a pediatric endocrinologist in the MGH Neuroendocrine Unit, who had a National Institutes of Health (NIH) R01 grant focused on hormones and bone health in young oligomenorrheic athletes and low body fat – another human model of energy deficit – to ask whether we could use stored blood samples to measure oxytocin levels. An MGH Claflin Distinguished Scholar Award, granted to support early-stage female investigators with parenting responsibilities, gave me critical flexible support that allowed me to pursue this line of research. My hypothesis was that in these athletes in energy deficit, similar to women with anorexia nervosa, oxytocin levels would be low and linked to markers of energy homeostasis as well as worse bone health. Madhu was enthusiastic about this project, the first of many productive collaborations. Consistent with our hypothesis, we found that oxytocin levels from individuals' pooled samples collected every 60 min overnight were low in oligomenorrheic athletes compared to controls, even after controlling for estradiol levels [17]. Lower fasting oxytocin levels were associated with lower body mass index, levels of irisin and FGF-21 (hormones that promote energy expenditure), and resting energy expenditure (controlled for lean mass) [20]. Further, lower overnight oxytocin levels were associated with impaired cortical and trabecular bone microarchitecture [17]. These data in a second model of energy deficit supported our findings in anorexia nervosa and set the stage for an ongoing Department of Defense randomized clinical trial (in collaboration with Madhu Misra (principal investigator, PI) and Ann Neumeyer, Medical Director at the MGH Lurie Center, who discovered that autism is associated with low bone mineral density) [29] of intranasal oxytocin (TNX-1900, Tonix Pharmaceuticals; New Jersey, USA) for bone health in children with autism, a condition associated with low levels of endogenous oxytocin.

Over the years through a series of studies in collaboration with the MGH Eating Disorders Clinical and Research Program (co-Directors, Kamryn Eddy, PhD, and Jennifer Thomas, PhD) we have increased our knowledge of the oxytocin system in females with anorexia nervosa. We showed that oxytocin levels were suppressed not just in women with current anorexia nervosa, but also in those with a history of anorexia nervosa who were normal- or overweight compared to similar weight controls with no eating disorder history [22]. Oxytocin suppression in these women could represent scar from chronic undernutrition, continued aberrant eating behaviors, failure to reach their individual ideal weights, or alternatively a trait characteristic. Lower fasting oxytocin levels were associated with more severe anxiety and depressive symptoms, suggesting that reduced oxytocinergic tone could contribute to psychopathology. Consistent with these data, we found that lower fasting oxytocin levels were correlated with increased severity of anxiety and depressive symptoms, as well as worse social emotional functioning in women with restrictive anorexia nervosa [24]. The relationships between oxytocin levels and anxiety and social emotional symptoms were not present in binge/purge-subtype anorexia nervosa, suggesting different pathophysiology or that purging behaviors mask a link between the oxytocin system and psychopathology by impacting peripheral oxytocin levels [24].

Discovery of an oxytocin deficient state in the context of energy deficit, associated with markers of energy homeostasis and severity of clinical sequelae raised the question of whether an intervention to increase oxytocin signaling would be useful therapeutically. The concern of this approach, of course, is that if oxytocin is anorexigenic and leads to weight loss, increasing oxytocin signaling in an energy deficit state could have devastating consequences. At the time I initially considered this question, studies in animal models had shown that oxytocin administration reduced caloric intake and body weight [8,9,30], but there were no studies in humans. This led me down the path of determining whether oxytocin impacts eating behavior in humans, with the idea that a negative study would support the safety of research administering oxytocin in anorexia nervosa, whereas a positive study showing that oxytocin reduces caloric intake in humans, as it does in animals, could lead to a potential intervention for obesity and disorders of excessive eating.

3. Oxytocin effects on eating behavior and metabolism in humans

When I raised the idea of conducting a translational research study investigating oxytocin effects on eating behavior with my mentor, Anne Klibanski, she encouraged me to write up a research protocol. I designed a randomized placebo-controlled crossover study of single dose intranasal oxytocin at a dose shown to have central effects in humans [31–34]. I recognized that effects of oxytocin could be sexually dimorphic and both sexes would need to be studied. Studying women would be complex given the effects of estradiol on the oxytocin system [35], so I decided to start with men. Since I had some funds through an MGH Claflin Scholar Award, and at that time NIH funding of our Clinical Research Center allowed junior investigators to receive free-of-charge

services, including nursing, blood draws, laboratory testing and bionutrition, I was able to start up the study. Later I received additional funding through NIH-funded Nutrition Obesity Research Centers (Boston and Harvard), allowing me to study 25 men across the weight spectrum. I had hoped to be the first to report on effects of intranasal oxytocin on eating behavior in humans with implications for obesity management, but before my study was complete, Ott et al. published a study of similar design to mine, showing no effects of 24 IU intranasal oxytocin on caloric intake at a test meal in normal weight men, though consumption of a palatable snack after the meal was reduced [36]. The same year, Zhang et al. reported substantial weight loss effects of 24 IU intranasal oxytocin given four times daily in a small study of adults with obesity [37]. In our study of men, after receiving a dose of oxytocin or placebo, participants ordered breakfast from a menu and were given double portions. I prepared myself for the possibility of negative results given the Ott study, and was excited to find that in our study, consistent with my hypothesis, oxytocin resulted in decreased caloric intake at the breakfast meal [38]. Further, oxytocin increased fat utilization assessed using indirect calorimetry and improved fasting insulin sensitivity, in line with findings in animals. The discordant results of our study and those of Ott's may have been related to the population studied. A later publication by the same group (Manfred Hallschmeid; Tubingen, Germany) found that oxytocin reduced caloric intake at a test meal in men with obesity, in contrast to their findings in those of normal weight [39]. Our study included men across the weight spectrum, and the inclusion of those with excess weight may have increased our ability to detect oxytocin effects on food intake, though statistically our findings held when controlling for body mass index. Later studies by others' confirmed that oxytocin reduced caloric intake in men as well as women [40].

To understand mechanisms for oxytocin effects, in a randomized placebo-controlled crossover study of single dose intranasal oxytocin (24 IU) in 10 men with overweight or obesity, we examined effects on functional magnetic resonance imaging (fMRI) activation and connectivity of brain circuitry involved in eating behavior using a visual food cue paradigm developed by my collaborator, neuroscientist Laura Holsen. Here we showed that while viewing images of high calorie foods compared to objects, oxytocin reduced activation of the ventral tegmental area (primary endpoint) and other reward related food motivation brain regions, as well as the hypothalamus (responsible for homeostatic control of feeding) [41], consistent with studies in rodents showing that oxytocin may reduce calorie intake through hedonic and homeostatic circuits [30,42–47]. Further, we found that oxytocin reduced functional connectivity between the ventral tegmental area and other food motivation brain regions when viewing high calorie foods (but not low-calorie foods or objects), indicating that asynchronous activation of these brain regions could underlie anorexigenic effects [48]. Franziska Plessow, a cognitive psychologist who joined my research team as a post doctoral fellow, provided expertise in examining the role of oxytocin on cognitive control over eating. We showed that oxytocin increased activation of areas of the brain responsible for cognitive control [41] and reduced impulsive behavior in an experimental task (Stop Signal) previously linked to eating [49]. (These data led to Franziska's postdoctoral fellow grant investigating intranasal oxytocin for attention deficit hyperactivity disorder (ADHD), and our provisional patent for the concept of using intranasal oxytocin to improve impulse control in ADHD). In collaboration with Novartis, we also leveraged samples from our prior randomized trial of single dose intranasal oxytocin on food intake in men to examine peripheral mechanisms of oxytocin effects. Here we showed that oxytocin modulates expression of circulating proteins involved in inflammation, immunity, and cell signaling pathways, and identified a specific cluster of these proteins impacted by oxytocin that were associated with subsequent reduced caloric intake at the test meal (manuscript under review). Taken together, these findings supported oxytocin as a potential novel therapeutic for obesity and disorders of excessive eating (e.g., binge eating disorder).

Based on these data, I designed a randomized controlled clinical trial to study the efficacy, safety and mechanisms of 8 weeks intranasal oxytocin (Syntocinon, Novartis/Mylan) 24 IU four times daily; prior to meals and at bedtime) for adults with obesity, which was funded by NIDDK [50]. The dosing regimen was based on studies of single dose intranasal oxytocin demonstrating engagement of relevant neurocircuitry with effects on impulse control and food intake, as well as a published pilot study of adults with obesity (9 receiving oxytocin) showing 9 kg weight loss at 8 weeks [37]. This was a challenging study to complete given comprehensive assessments (e.g., MRI's for functional neuroimaging and fat depots, test meals for eating behavior, serial blood draws in fasting and fed states) and the difficulties of recruiting and retaining study participants with the advent of COVID-19. It was a disappointment – but important – to find that this regimen of intranasal oxytocin did not impact body weight (primary endpoint), resting energy expenditure, or body composition (key secondary endpoints) [51]. Interestingly, even though we held the morning dose of oxytocin prior to examining caloric intake at our study test meal and the evening dose would have been out of their system, those receiving oxytocin ate fewer calories (key secondary endpoint). Nonetheless, we did not see a difference with oxytocin in self-reported caloric intake assessed with 4-day food diaries. This discrepancy could be related to reduced accuracy of self-report versus the experimental task in assessing calories consumed, or the greater need for cognitive control over eating in the test meal where participants were given double portions of the food ordered off of a menu. It could be that people with disorders associated with difficulties engaging cognitive control over eating, such as those with binge eating disorder, would be particularly responsive to oxytocin-based therapeutics to reduce caloric intake. We are currently conducting a clinical trial of intranasal oxytocin (TNX-1900, Tonix Pharmaceuticals) for binge eating disorder. Another signal of interest in the trial was the finding that oxytocin improved self-reported mental health quality of life, despite the fact that individuals with current psychiatric disorders were excluded from participation in the study. Whether oxytocin improves psychopathology in people with mental health disorders will be an important question for future studies. There are several possible reasons for our overall "negative" trial with no effect on body weight, and our study may provide insights for future research [51]. For example, longer duration of oxytocin administration may be needed to see weight loss, a different drug regimen (dose and/or frequency) or oxytocin-based drug (e.g., formulation with magnesium [52]; longer-acting, specific oxytocin receptor agonist [53]) may be more effective. Future studies using novel formulations and oxytocin receptor agonists will be of great interest. We are now investigating a potentiated intranasal oxytocin with magnesium (TNX-1900, Tonix Pharmaceuticals) in our clinical trials, including in a study of adolescents with obesity (multi-PI R01 with Madhu Misra and Miriam Bredella).

4. Oxytocin deficiency in pituitary disease

As an endocrine fellow providing clinical care for patients with hypothalamic and pituitary disease, I was struck that while we replace vasopressin in patients with arginine vasopressin (AVP) deficiency (previously known as diabetes insipidus), no oxytocin deficient state had yet been identified. This seemed particularly important given residual symptoms and lower quality of life in patients with hypopituitarism despite standard of care hormone replacement. A few years later, Dr. Karen Miller, a mentor over the years who is now our Neuroendocrine Unit Chief, offered me the opportunity to measure oxytocin levels in patients with hypopituitarism compared to healthy controls using stored fasting blood samples from a past study. Our preliminary data was disappointing in that fasting oxytocin levels were not lower in those with hypopituitarism; however, this provided insights into our design of a cross-sectional study to identify and clinically characterize oxytocin deficiency in patients with pituitary disease. It can be challenging to

secure funding to investigate hypopituitarism, as this is a rare disease. An MGH Polsky Scholar Award, subsequent philanthropic gifts, and small grants provided critical funds that made this line of research possible. Rather than looking at oxytocin levels across patients with all types of hypopituitarism, we focused on those patients with pituitary disease most likely to have oxytocin deficiency based on the anatomy, i.e., those with AVP deficiency, as oxytocin and AVP are produced, stored, and released in the same locations. We decided to study men given the known effects of estrogen status on endogenous oxytocin levels, and the variable estrogen levels in women with hypopituitarism. We compared men with hypopituitarism and AVP deficiency to men with similar anterior pituitary deficiencies and hormone replacement but no AVP deficiency, as well as men with no pituitary disease. We strategically recruited groups of similar age and body mass index, given effects of these factors on endogenous oxytocin levels. Since our prior data showed that peripheral oxytocin secretion is pulsatile in men with approximately two secretory bursts per hour [25], we decided not to rely on measurement of oxytocin at a single timepoint. Instead, we sampled fasting blood for oxytocin serially every 5 min for an hour and pooled each individual's samples to capture basal and pulsatile secretion. Using this approach, we showed for the first time that circulating oxytocin levels were low in patients with AVP deficiency compared to those with similar anterior pituitary deficiencies but no AVP deficiency as well as healthy individuals without pituitary disease [21]. Further, the men with AVP deficiency also had worse anxiety and depressive symptoms, social emotional functioning difficulties, and self-reported mental health than healthy controls. We also found that lower levels of oxytocin were associated with lower bone mineral density at the spine, femoral neck and total hip, as well as unfavorable hip geometry and strength, in men with AVP deficiency [21]. Overall, our findings were consistent with a clinically relevant oxytocin deficient state in men with AVP deficiency, with features seen in other oxytocin deficient states, e.g., in the context of energy deficit. A study by the group of Mirjam Christ-Crain (Basel, Switzerland) later showed that MDMA stimulated oxytocin release and reduced anxiety symptoms in healthy individuals but not those with AVP deficiency, confirming oxytocin deficiency in this population [54]. These studies support the possibility of oxytocin replacement to improve the physical and mental health as well as quality of life for individuals who have pituitary disease and oxytocin deficiency.

Ongoing research is aimed at developing and validating provocative testing for the diagnosis of oxytocin deficiency. We and others have examined whether physiologic and pharmacologic stimuli for oxytocin release in animal models translate to humans, with mixed results. Our studies did not support a mixed meal [55], oral salt load, or angiotensin II [56], and Mirjam Christ-Crain's studies did not support arginine, macimorelin, or hypertonic saline [57] as candidates for provocative tests to diagnose oxytocin deficiency. Insulin-induced hypoglycemia stimulates oxytocin release in healthy adults [13,58,59], but has not yet been fully evaluated as a provocative test in hypopituitarism. Oral estrogen/progestin increases peripheral oxytocin levels in both men and women [13,60], and we are investigating effects in individuals with AVP deficiency. Anna Aulinas (Barcelona, Spain), a former postdoctoral fellow in my lab, is studying the potential of corticotrophin releasing hormone, melatonin, and a glucagon-like peptide-1 agonist (exenatide), for diagnosis of oxytocin deficiency.

We are also piloting studies to examine dose effects of intranasal oxytocin on behavioral markers of anxiety, depression, and social emotional functioning, as well as bone turnover markers in adults with AVP deficiency. Randomized, placebo-controlled trials will be needed to determine whether therapeutic oxytocin administration is safe and beneficial in individuals with hypopituitarism and oxytocin deficiency.

5. Translation to patient care: challenges, opportunities

The goal of my research program is to improve our understanding of oxytocin in human physiology and pathophysiology to advance clinical care. Based on studies in animal models and early human data, oxytocin-based therapeutics hold promise in neuropsychiatric and metabolic disorders [14,53,61]. However, there are challenges to overcome for these early findings to translate to patient care. Development and validation of improved measurement techniques to assess levels of oxytocin and metabolized products, which may also be biologically active, will be key in moving the field forward. Normal ranges will need to be established in both sexes across the lifespan. A diagnostic provocative test for oxytocin deficiency will be useful for identifying those who could most benefit from treatment. Future studies improving our understanding of oxytocin secretory patterns in human physiology and the relation to clinical endpoints will be helpful in guiding development and application of therapeutics. Basal levels and pulses of oxytocin may have different effects. For example, we found that pulse characteristics of oxytocin were highly correlated to social emotional functioning measures in a small sample of healthy men [25]. In men with AVP deficiency, in contrast, single timepoint circulating oxytocin (likely reflecting basal levels), but not 1-h pooled samples (capturing on average two pulses per hour) [25] were associated with bone health [21]. Based on these data, one might consider an intervention resulting in bursts of short-acting oxytocin several times per hour to improve social emotional functioning, and a lower dose, long-acting oxytocin analog to raise basal levels for treatment of osteopenia. The optimal regimen for oxytocin replacement in deficient patients would mirror normal physiologic patterns. However, physiologic data related to oxytocin secretion in humans is currently lacking. Mechanistic investigations are critical to understand whether central or peripheral oxytocin signaling drives specific effects to guide drug development for different indications. Pharmacodynamic studies will be important for establishing optimal doses. To determine safety and efficacy of oxytocin-based therapeutics for different indications and identify individuals who are most responsive, clinical trials will be critical. For rare diseases, such as oxytocin deficiency in individuals with hypopituitarism, multicenter trials will be needed.

6. Progress through community and collaboration

A decade ago, I founded the Harvard Interdisciplinary Oxytocin Research Initiative, which started with a handful of researchers in the Boston area interested in oxytocin, and has expanded to include more than 50 researchers worldwide representing a variety of fields and methodologies. Some of us are physician scientists, others are PhD's. Some do fundamental research, others clinical. We work on a variety of topics, e.g., neuropsychiatric disorders, inflammation, metabolism, microbiome, social behaviors, genetics, and analytic methods. What we have in common is a passion for understanding the oxytocin system and using this knowledge to improve health. At our monthly meetings, investigators, some well-established, others at the beginning of their careers, move our field forward by sharing their research findings, novel ideas, and specialized knowledge. These interactions have broadened my understanding of oxytocin and enriched my research. For example, James "Ernie" Blevins, whose mechanistic preclinical research on oxytocin in energy homeostasis has been instrumental in informing translational studies in humans [61], and I have exchanged ideas, turned to each other for feedback on grants and manuscripts, and shared opportunities (e.g., speaking engagements, writing articles). Our most senior member, C. Sue Carter, a pioneer in oxytocin research [62], has been particularly influential on my career, generously sharing her experience and hypotheses, making introductions to experts in the field, and identifying funding for collaborative projects. Through this initiative, it has become clear to me that outstanding scientists worldwide are working towards addressing many of most important unanswered questions in the field, and that a collaborative approach will accelerate our progress.

CRediT authorship contribution statement

Elizabeth A. Lawson: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

EAL receives grant support and research study drug from Tonix Pharmaceuticals and receives royalties from UpToDate. EAL is also supported by NIH R01DK124223, R01MH128246, R61MH129331, K24MH120568, P30DK040561; Department of Defense AR220116 HT9425-23-1-0219; Templeton Foundation; Women's Wellness Foundation; and philanthropic gifts. EAL and/or immediate family member holds stock in Thermo Fisher Scientific, Zoetis, Danaher Corporation, Intuitive Surgical. EAL is an inventor on US provisional patent applications no. 63/413,657 (Oxytocin-based therapeutics for bone health in individuals with autism) and no. 63/467,980 (Oxytocin-based therapeutics to improve cognitive control in individuals with attention deficit hyperactivity disorder).

Acknowledgements

EAL would like to thank her collaborators, trainees, mentors, study staff, study participants, and those who provided funds to make this research possible.

References

[1] E.A. Lawson, K.K. Miller, in: *Anorexia Nervosa: Endocrine Complications and Their Management* C. RF, Wolters Kluwer: UpToDate, 2022.
[2] C. Camerino, Low sympathetic tone and obese phenotype in oxytocin-deficient mice, Obesity 17 (5) (2009) 980–984.
[3] Y. Takayanagi, et al., Oxytocin receptor-deficient mice developed late-onset obesity, Neuroreport 19 (9) (2008) 951–955.
[4] R.C. Mantella, et al., Female oxytocin-deficient mice display enhanced anxiety-related behavior, Endocrinology 144 (6) (2003) 2291–2296.
[5] H. Matsushita, et al., Oxytocin mediates the antidepressant effects of mating behavior in male mice, Neurosci. Res. 68 (2) (2010) 151–153.
[6] J.T. Winslow, T.R. Insel, The social deficits of the oxytocin knockout mouse, Neuropeptides 36 (2–3) (2002) 221–229.
[7] R. Tamma, et al., Oxytocin is an anabolic bone hormone, Proc. Natl. Acad. Sci. U. S. A. 106 (17) (2009) 7149–7154.
[8] G. Zhang, D. Cai, Circadian intervention of obesity development via resting-stage feeding manipulation or oxytocin treatment, Am. J. Physiol. Endocrinol. Metab. 301 (5) (2011) E1004–E1012.
[9] R. Arletti, A. Benelli, A. Bertolini, Influence of oxytocin on feeding behavior in the rat, Peptides 10 (1) (1989) 89–93.
[10] C.S. Carter, et al., Oxytocin and social bonding, Ann. N. Y. Acad. Sci. 652 (1992) 204–211.
[11] C. Elabd, et al., Oxytocin controls differentiation of human mesenchymal stem cells and reverses osteoporosis, Stem Cell. 26 (9) (2008) 2399–2407.
[12] M.A. Demitrack, et al., CSF oxytocin in anorexia nervosa and bulimia nervosa: clinical and pathophysiologic considerations, Am. J. Psychiatr. 147 (7) (1990) 882–886.
[13] P. Chiodera, et al., Effect of estrogen or insulin-induced hypoglycemia on plasma oxytocin levels in bulimia and anorexia nervosa, Metabolism 40 (11) (1991) 1226–1230.
[14] F. Plessow, K.T. Eddy, E.A. Lawson, The neuropeptide hormone oxytocin in eating disorders, Curr. Psychiatr. Rep. 20 (10) (2018) 91.
[15] E.A. Lawson, et al., Hypercortisolemia is associated with severity of bone loss and depression in hypothalamic amenorrhea and anorexia nervosa, J. Clin. Endocrinol. Metab. 94 (12) (2009) 4710–4716.
[16] E.A. Lawson, et al., Decreased nocturnal oxytocin levels in anorexia nervosa are associated with low bone mineral density and fat mass, J. Clin. Psychiatry 72 (11) (2011) 1546–1551.
[17] E.A. Lawson, et al., Nocturnal oxytocin secretion is lower in amenorrheic athletes than nonathletes and associated with bone microarchitecture and finite element analysis parameters, Eur. J. Endocrinol. 168 (3) (2013) 457–464.
[18] M. Schorr, et al., Oxytocin and its relationship to body composition, bone mineral density, and hip geometry across the weight spectrum, J. Clin. Endocrinol. Metab. 102 (8) (2017) 2814–2824.
[19] A. Aulinas, et al., Low plasma oxytocin levels and increased psychopathology in hypopituitary men with diabetes insipidus, J. Clin. Endocrinol. Metab. 104 (8) (2019) 3181–3191.
[20] E.A. Lawson, et al., Oxytocin secretion is related to measures of energy homeostasis in young amenorrheic athletes, J. Clin. Endocrinol. Metab. 99 (5) (2014) E881–E885.
[21] A. Aulinas, et al., Lower oxytocin levels are associated with lower bone mineral density and less favorable hip geometry in hypopituitary men, Neuroendocrinology 111 (1–2) (2021) 87–98.
[22] Y. Afinogenova, et al., Low fasting oxytocin levels are associated with psychopathology in anorexia nervosa in partial recovery, J. Clin. Psychiatry 77 (11) (2016) e1483–e1490.
[23] C. Schmelkin, et al., Low oxytocin levels are related to alexithymia in anorexia nervosa, Int. J. Eat. Disord. 50 (11) (2017) 1332–1338.
[24] F. Plessow, et al., Low oxytocin levels are broadly associated with more pronounced psychopathology in anorexia nervosa with primarily restricting but not binge/purge eating behavior, Front. Endocrinol. 13 (2022) 1049541.
[25] C. Baskaran, et al., Oxytocin secretion is pulsatile in men and is related to social-emotional functioning, Psychoneuroendocrinology 85 (2017) 28–34.
[26] A.S. Begin, et al., Biomarkers of clinician burnout, J. Gen. Intern. Med. 37 (2) (2022) 478–479.
[27] E.A. Lawson, The effects of oxytocin on eating behaviour and metabolism in humans, Nat. Rev. Endocrinol. 13 (12) (2017) 700–709.
[28] E.L. MacLean, et al., Challenges for measuring oxytocin: the blind men and the elephant? Psychoneuroendocrinology 107 (2019) 225–231.
[29] A.M. Neumeyer, et al., Bone density in peripubertal boys with autism spectrum disorders, J. Autism Dev. Disord. 43 (7) (2013) 1623–1629.
[30] G.J. Morton, et al., Peripheral oxytocin suppresses food intake and causes weight loss in diet-induced obese rats, Am. J. Physiol. Endocrinol. Metab. 302 (1) (2012) E134–E144.
[31] M. Heinrichs, et al., Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress, Biol. Psychiatr. 54 (12) (2003) 1389–1398.
[32] G. Domes, et al., Oxytocin attenuates amygdala responses to emotional faces regardless of valence, Biol. Psychiatr. 62 (10) (2007) 1187–1190.
[33] G. Domes, et al., Oxytocin improves "mind-reading" in humans, Biol. Psychiatr. 61 (6) (2007) 731–733.
[34] T. Baumgartner, et al., Oxytocin shapes the neural circuitry of trust and trust adaptation in humans, Neuron 58 (4) (2008) 639–650.
[35] G. Gimpl, F. Fahrenholz, The oxytocin receptor system: structure, function, and regulation, Physiol. Rev. 81 (2) (2001) 629–683.
[36] V. Ott, et al., Oxytocin reduces reward-driven food intake in humans, Diabetes 62 (10) (2013) 3418–3425.
[37] H. Zhang, et al., Treatment of obesity and diabetes using oxytocin or analogs in patients and mouse models, PLoS One 8 (5) (2013) e61477.
[38] E.A. Lawson, et al., Oxytocin reduces caloric intake in men, Obesity 23 (5) (2015) 950–956.
[39] M.S. Spetter, et al., Oxytocin curbs calorie intake via food-specific increases in the activity of brain areas that process reward and establish cognitive control, Sci. Rep. 8 (1) (2018) 2736.
[40] V. Burmester, S. Higgs, P. Terry, Rapid-onset anorectic effects of intranasal oxytocin in young men, Appetite 130 (2018) 104–109.
[41] F. Plessow, et al., Effects of intranasal oxytocin on the blood oxygenation level-dependent signal in food motivation and cognitive control pathways in overweight and obese men, Neuropsychopharmacology 43 (3) (2018) 638–645.
[42] L. Kerem, E.A. Lawson, The effects of oxytocin on appetite regulation, food intake and metabolism in humans, Int. J. Mol. Sci. 22 (14) (2021).
[43] Y. Maejima, et al., Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass, Aging (Albany NY) 3 (12) (2011) 1169–1177.
[44] Y. Maejima, et al., Nasal oxytocin administration reduces food intake without affecting locomotor activity and glycemia with c-Fos induction in limited brain areas, Neuroendocrinology 101 (1) (2015) 35–44.
[45] K. Mullis, K. Kay, D.L. Williams, Oxytocin action in the ventral tegmental area affects sucrose intake, Brain Res. 1513 (2013) 85–91.
[46] H.S. Wald, et al., NTS and VTA oxytocin reduces food motivation and food seeking, Am. J. Physiol. Regul. Integr. Comp. Physiol. 319 (6) (2020) R673–R683.
[47] J.M. Ho, et al., Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats, Endocrinology 155 (8) (2014) 2845–2857.
[48] L. Kerem, et al., Oxytocin reduces the functional connectivity between brain regions involved in eating behavior in men with overweight and obesity, Int. J. Obes. 44 (5) (2020) 980–989.
[49] F. Plessow, et al., Oxytocin administration increases proactive control in men with overweight or obesity: a randomized, double-blind, placebo-controlled crossover study, Obesity 29 (1) (2021) 56–61.
[50] M.L. Wronski, et al., A randomized, double-blind, placebo-controlled clinical trial of 8-week intranasal oxytocin administration in adults with obesity: rationale, study design, and methods, Contemp. Clin. Trials 122 (2022) 106909.
[51] F. Plessow, et al., Intranasal oxytocin for obesity, NEJM Evidence 3 (5) (2024) EVIDoa2300349.
[52] V.N. Bharadwaj, et al., Impact of magnesium on oxytocin receptor function, Pharmaceutics 14 (5) (2022).
[53] C.T. Elfers, et al., Novel long-acting oxytocin analog with increased efficacy in reducing food intake and body weight, Int. J. Mol. Sci. 23 (19) (2022).
[54] C. Atila, et al., Oxytocin in response to MDMA provocation test in patients with arginine vasopressin deficiency (central diabetes insipidus): a single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial, Lancet Diabetes Endocrinol. 11 (7) (2023) 454–464.
[55] A. Aulinas, et al., Endogenous oxytocin levels in relation to food intake, menstrual phase, and age in females, J. Clin. Endocrinol. Metab. 104 (4) (2019) 1348–1356.
[56] S. Srinivasa, et al., Oxytocin response to controlled dietary sodium and angiotensin II among healthy individuals, Am. J. Physiol. Endocrinol. Metab. 315 (4) (2018) E671–E675.

[57] C.O. Sailer, et al., Oxytocin levels in response to pituitary provocation tests in healthy volunteers, Eur. J. Endocrinol. 185 (3) (2021) 355–364.
[58] P. Chiodera, et al., Hypoglycemia-induced arginine vasopressin and oxytocin release is mediated by glucoreceptors located inside the blood-brain barrier, Neuroendocrinology 55 (6) (1992) 655–659.
[59] P. Chiodera, et al., Oxytocin response to challenging stimuli in elderly men, Regul. Pept. 51 (2) (1994) 169–176.
[60] J.A. Amico, S.M. Seif, A.G. Robinson, Oxytocin in human plasma: correlation with neurophysin and stimulation with estrogen, J. Clin. Endocrinol. Metab. 52 (5) (1981) 988–993.
[61] S.E. McCormack, J.E. Blevins, E.A. Lawson, Metabolic effects of oxytocin, Endocr. Rev. 41 (2) (2020) 121–145.
[62] C.S. Carter, Close encounters with oxytocin, Compr Psychoneuroendocrinol 15 (2023) 100189.