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REVIEW ARTICLE

Oxytocin and Eating Disorders: A Narrative Review on Emerging Findings and Perspectives

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Abstract: ***Background*:** The hypothalamic neuropeptide oxytocin regulates reproductive behavior and mother-infant interaction, and conclusive studies in humans indicate that oxytocin is also a potent modulator of psychosocial function. Pilot experiments have yielded first evidence that this neuropeptide moreover influences eating behavior.

***Methods*:** We briefly summarize currently available studies on the involvement of the oxytocin system in the pathophysiology of eating disorders, as well as on the effects of oxytocin administration in patients with these disorders.

***Results*:** Brain administration of oxytocin in animals with normal weight, but also with diet-induced or genetically induced obesity, attenuates food intake and reduces body weight. In normal-weight and obese individuals, acute intranasal oxytocin delivery curbs calorie intake from main dishes and snacks. Such effects might converge with the poignant social and cognitive impact of oxytocin to also improve dysfunctional eating behavior in the therapeutic context. This assumption has received support in first studies showing that oxytocin might play a role in the disease process of anorexia nervosa. In contrast, respective experiments in patients with bulimia nervosa and binge eating disorder are still scarce.

***Conclusions*:** We propose a framework of oxytocin's role and its therapeutic potential in eating disorders that aims at integrating social and metabolic aspects of its pharmacological profile, and ponder perspectives and limitations of oxytocin use in the clinical setting.

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1. INTRODUCTION

Recently, there has been increasing interest in the role of oxytocin in the development and maintenance of a broad spectrum of mental disorders [1]. While initially and primarily known for its role in interpersonal relationships, including sexuality, mother-infant bonding and interpersonal trust, oxytocin has turned out to directly or indirectly contribute to a range of other psychological and physiological functions in humans, including social cognition, and also eating behavior and metabolism [2, 3]. Patients with mental disorders – including eating disorders across the whole weight spectrum – often show impairments in one or more of these systems. Against this backdrop, it may be hypothesized that oxytocin plays a role in the connection between psychosocial functions and ingestive behavior [4, 5], and that respective mutual impairments stem at least in part from alterations in oxytocin pathways.

In the present narrative review, after a short introduction on the physiology of the oxytocin system, we summarize current evidence on oxytocin's role in the regulation of food intake and on respective changes in populations with disturbed eating behavior and with eating disorders. We outline different potential pathways in which oxytocin might contribute to the development and maintenance of eating disorders and discuss the potential of oxytocin as a treatment agent for patients suffering from eating disorders.

2. THE NEUROHORMONE OXYTOCIN

2.1. Physiology

The nine-amino acid neuropeptide oxytocin is mainly produced in the paraventricular nucleus (PVN) and the su-

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praoptic nucleus of the hypothalamus [6]. Roughly 40% of PVN oxytocin neurons project to the pituitary gland and central nervous structures including the brainstem. Notably, around ten percent of PVN oxytocin neurons connect to three brainstem areas with a major role in the regulation of eating behavior, *i.e*., the nucleus tractus solitarius, the dorsal motor nucleus of the vagus nerve, and the area postrema [7, 8]. Oxytocin concentrations in the brain by far exceed those in blood, and it has been assumed that the peptide does not readily cross the blood-brain barrier to re-enter the brain compartment [9], although recent data obtained in monkeys suggest otherwise [10] (see paragraph 2.2). Oxytocin's half-life in the brain is three times as long as in the periphery (19 vs. 6 minutes) [11, 12]. These physiological features are very much in line with the assumption that the hormone acts as a relevant modulator of central nervous function [13].

Oxytocin binds to a G-protein-coupled receptor [14] that is expressed throughout the brain [15], among others in regions like hypothalamus, amygdala, anterior cingulate cortex, olfactory nucleus, and the limbic system [16]. Serotonin has been found to increase oxytocin concentrations [17] while dopamine interactions with oxytocin can modulate the activity of the reward circuitry of the brain [18, 19]. These findings might be of particular relevance for behavioral disorders like autism and depression, but also for eating disorders [20]. Secretion of oxytocin in the body periphery has been observed in myenteric and submucous ganglia and nerve fibres of the human gastrointestinal tract [21]. The best understood physiological function of centrally released oxytocin primarily concerns the female reproductive system. The uterus displays enhanced oxytocin sensitivity before birth, and receptor density increases during labor [22]. After parturition, the baby triggers oxytocin secretion by sucking on the mother's nipple, thereby stimulating lactation, which is one of the main physiological effects of oxytocin. Considering that the prevalence of most eating disorders displays a preponderance in women, it is tempting to speculate that because of the particular functional relevance of oxytocin in the female organism, changes in oxytocin pathways contribute to dysfunctional eating patterns and that interventions aimed at these pathways hold a certain therapeutic potential.

2.2. Intranasal Oxytocin Administration

Since the peripheral administration of hormones to target the brain can be associated with peripheral (side) effects, and brain uptake may be limited by receptor-mediated, saturable mechanisms of transport across the blood-brain barrier [23], the intranasal administration route has turned out as a feasible tool to study the contribution of (neuro)peptidergic messengers to human brain function. In humans, intranasally administered peptides reach the central nervous compartment within around 45 min [24]. Intra-neuronal transport from the nose to the olfactory bulb would take several hours [25], which makes it more likely that intranasally administered neuropeptides reach the CNS *via* extra-neuronal pathways. They may bypass the BBB paracellularly by diffusing into the subarachnoidal space across the olfactory epithelia and through intercellular clefts between sustentacular cells and olfactory neurons [26]. Transport along cranial and trigeminal nerve branches may support this path of uptake [27].

Studies on the intranasal administration of (mainly 24-30 IU) oxytocin in human subjects show that peak plasma concentrations are reached around 10-90 min after application (*e.g*., [28, 29]) and that the strongest accumulation in cerebrospinal fluid (CSF) emerges 60 min after administration [30]. In recent sophisticated experiments in rhesus macaques [10], labeled (exogenous) and endogenous oxytocin were assessed by quantitative mass spectrometry after intranasal and intravenous delivery. It was found that oxytocin uptake into CSF is not improved after intranasal compared to intravenous administration, but that systemic exposure due to plasma uptake is strongly decreased in the former case. Intranasal oxytocin delivery is easy to apply and generally well tolerated [31] and has been used to support lactation and labor induction (*i.e*., to target peripheral organ systems). The use of intranasal oxytocin to modulate brain function in clinical settings may need some technical optimization, especially with regard to absorption despite degradation by the nasal mucosa [32], and intense research efforts will be necessary to investigate safety and side effects of higher doses and extended administration periods.

3. OXYTOCIN AS A REGULATOR OF EATING BEHAVIOR

3.1. Studies in Animals

Evidence for a role of oxytocin in the control of eating behavior was first gathered in animal experiments. Lesions of the PVN, one of main sites of oxytocin production, stimulate food intake and increase body weight [33]. Vice versa, administering oxytocin *via* intraperitoneal or intracerebroventricular injections attenuate food intake [34, 35]. Notably, comparable effects were found in animals with genetically or diet-induced obesity (DIO) [36-42]. Oxytocin- or oxytocin receptor-deficient mice show modest, late-onset obesity even in the absence of changes in food intake [43, 44], which might be due to enhancing effects of oxytocin on energy expenditure [37, 45-47]. Oxytocin has turned out to be a downstream mediator of the effects of leptin [48], an anorexigenic product of white fat cells that signals to the brain how much energy is stored as body fat. Leptin is a predominant player in the maintenance of energy homeostasis also because of its stimulating effect on energy expenditure [49]. In rats, oxytocin-expressing neurons of the PVN contribute to the inhibitory impact of leptin on food intake [50]. In a series of animal experiments, Yada and coworkers have demonstrated that oxytocin activates pro-opiomelanocortin neurons in the nucleus tractus solitarius of the brainstem [39] as well as the hypothalamic arcuate nucleus [51], thereby triggering a key anorexigenic signal in the homeostatic control of eating. While the ablation of oxytocin neurons in adult animals kept on a regular diet does not affect body weight, food intake and energy expenditure, these mice nevertheless display reduced sensitivity to the anorexigenic effect of leptin and are more likely to develop DIO *via* reductions in energy expenditure [46]. Hypothalamic oxytocinergic neurons connect to pivotal parts of the brain reward circuit such as the nucleus accumbens (NAcc) [52], and oxytocin administration attenuates dopamine signaling in NAcc and striatum [53]. Therefore, the peptide may also attenuate eating behavior by modulating reward-related signaling. This

notion has received support in experiments in humans that are discussed in the following paragraph.

3.2. Studies in Humans

The first study to address the impact of intranasal oxytocin on ingestive behavior showed that in normal-weight male subjects, the peptide decreases the consumption of palatable snacks (in this case chocolate cookies) in the aftermath of ad-libitum breakfast intake, *i.e.*, in the postprandial period when eating can be assumed to be primarily reward-driven [54]. Preceding breakfast intake in the fasted state was not altered, but endocrine stress axis activity was suppressed by oxytocin [54], an effect in accordance with experiments in humans [55] and animals [37, 42]. Signs of an oxytocin-induced enhancement in glucose tolerance in this study have been confirmed in systematic investigations: oxytocin administered intranasally to fasted young men before an oral glucose tolerance test induced pronounced increases in beta-cell responsivity and glucose tolerance [56]. When the effect of oxytocin on food intake was compared between normal-weight and obese men [57], cookie intake was likewise reduced in the obese participants. Of note, the obese men moreover reduced breakfast size after oxytocin administration, showing a decrease in hunger-driven calorie intake that was absent in normal-weight humans. Oxytocin-induced reductions in fasted-state breakfast consumption were found in obese, but also normal-weight subjects in related studies by the group of Elizabeth Lawson [58].

That obese animals and humans display intact (or even enhanced) sensitivity to the anorexigenic impact of oxytocin (*e.g.*, [37, 38, 40, 57]) may be due to relatively increased cholesterol levels in obesity boosting high-affinity binding of oxytocin to its receptor [15, 59]. The notion that oxytocin signaling per se is altered in obesity is supported by links between the oxytocin receptor gene and body weight [60, 61]. Circulating oxytocin concentrations have been found to be higher [62, 63], unchanged [64] or decreased [65] in obese compared to normal-weight subjects. Since parameters such as sex, age, BMI and blood glucose status of the subjects vary across these studies, it seems that work in larger samples will be necessary to come to more definite conclusions. Patients suffering from Prader-Willi syndrome, which is hallmarked by hyperphagic obesity as a consequence of persistent food craving, display a 40% reduction in the number and size of oxytocin neurons [66]. While eight-week intranasal oxytocin administration to such patients did not lower body weight or improve psychosocial function [67], young children with the syndrome displayed enhanced social and food-related behavior after a four-week oxytocin intervention [68]. The reported basic and (pre-)clinical results, although limited in number, have sparked some interest in the role of oxytocin as an anorexigenic factor in healthy humans and, in particular, in patients suffering from disturbed eating behavior.

4. WHY STUDY OXYTOCIN FUNCTION IN EATING DISORDERS?

Taking a closer look at typical symptoms of eating disorders, assumptions of current explanatory models and the many psychophysiological aspects of oxytocin as shortly outlined above, different potential pathways emerge by which oxytocin might contribute to the etiology and maintenance of eating disorders. While there are certainly more areas that might be of relevance in this regard, here we focus on two major aspects, *i.e.*, processes associated with (a) attachment and (b) social cognition. Importantly, these pathways may be mutually intertwined and might interact with each other.

4.1. Attachment Behavior and Mother-Infant Interactions

Insecure attachment and adverse attachment experiences have been discussed as risk factors for the development of eating disorders. Two recent reviews support this hypothesis by showing higher levels of attachment insecurity in individuals with eating disorders and eating disorder pathology in adulthood [69] as well as in childhood and adolescence [70] – although these predominantly cross-sectional and correlative data cannot be interpreted in terms of causality. Of note, attachment difficulties have been reported in a range of other mental disorders and hence do not represent a (putative) risk factor that is unique for the etiopathology of eating disorders. Yet, to a certain extent attachment might play a specific and complex role in the development of eating disorders as – especially in early infancy – a significant part of bonding activity takes place around (breast) feeding, and eating interactions and bonding are amongst others established and experienced within these feeding / eating situations.

Early mother-infant interactions and attachment difficulties might also represent a potential pathway that adds to an intergenerational perpetuation of eating disorders. Studies have shown that women with an eating disorder have more difficulties feeding their children and interacting with them [71], and they have general problems adjusting to motherhood [72].

Oxytocin might play a crucial role in this putative link between attachment and eating. As outlined above, oxytocin has long been known to play a crucial role in bonding behavior and attachment, *e.g.*, it increases positive parent-child interactions and fosters sensitivity and synchrony [73]. Moreover, it is released during breast feeding and is thus involved in the regulation of a behavior that closely interties the regulation of both, the mother-child social relationship and eating behavior.

An earlier neurodevelopmental model of anorexia nervosa by Janet Treasure and colleagues [74] has already integrated (insecure) attachment as a putative early vulnerability factor in the etiology of this eating disorder. Interestingly, the authors also briefly mention that oxytocin may be involved in the response to social stress, but do not go into further detail on this hormone. However, they also ponder potential psychobiological mechanisms underlying the relationship between attachment insecurity and eating disorder pathology. These putative mechanisms endorse that adverse attachment experiences in early life might modulate the stress response system, *i.e.*, result in hyperactivity of the hypothalamus-pituitary-adrenal axis, leading to problems in emotional processing and self-regulation. Eventually, dysfunctional eating behavior might represent an attempt to

regulate emotions and stress. This presumed mechanism represents a close link to processes of social cognition which are also modulated by oxytocin (see 4.2.). Although originally formulated for the development of anorexia nervosa, the assumptions of this model might also explain mechanisms underlying eating disorders associated with binge eating, including bulimia nervosa and binge eating disorder. Thus, difficulties in emotion regulation have been found to trigger binge eating in patients with binge eating disorder [75].

4.2. Social Cognition

Social cognition is an umbrella term which includes a variety of processes and competencies that are related to the processing, evaluation and application of information related to other individuals and social situations. Subcomponents *e.g*. include emotional recognition or the understanding of one's own and others' mental states. Patients with eating disorders and obesity have been found to show impairments in a range of subcompetencies of social cognition [76, 77]. These impairments contribute to profound problems in interpersonal function and have been discussed as a putative developmental / maintenance mechanism of eating disorders [78, 79]. In their cognitive-interpersonal maintenance model of anorexia nervosa, Treasure and Schmidt [79] have integrated impaired social processes as one central maintenance factor of anorexia nervosa. The model moreover assumes, as these socio-emotional problems might also partly run in families, that they contribute to difficult interpersonal communication within affected families, which additionally maintains the disorder. The authors also mention the putative role of dysregulated oxytocin function as a potential contributing factor to impaired social cognition in anorexia nervosa [79].

Not only dysfunctional attachment experiences (see 4.1.), but also difficulties in the field of social cognition have been likewise reported in other mental disorders. But once again, they might play a specific and complex role in the development of eating disorders, as eating often takes place in social contexts and the social context itself strongly influences our eating behavior [5]. Patients affected by eating disorders often generally suffer from social withdrawal, and they often especially withdraw from social eating contexts and rather eat alone, which might partly be due to shame associated with overeating during binge eating episodes. Hence, difficulties in interpersonal functioning and socio-emotional processing might be closely intertwined with dysfunctional eating.

Oxytocin is a neuroendocrine key player in the regulation of social relationships, and hence, it is not surprising that it also seems to play a role in social cognition. However, its effects on socio-emotional processing seem very complex and might strongly depend on the social context, *i.e*., on intra- and intergroup circumstances and the evaluation of the safety of the situation [80, 81]. Evidence from studies relying on intranasal oxytocin administration suggests that the hormone increases emotion recognition, expression of positive emotions, social recognition, social memory, empathy and interpersonal trust [2, 82] and decreases attention to threat and increases attention to positive emotions (*i.e*., happiness) [83].

5. EMPIRICAL FINDINGS ON OXYTOCIN (DYS)FUNCTION IN EATING DISORDERS

While studies investigating oxytocin function in eating disorders are still rare, they have used different methodological approaches. These range from the assessment of baseline oxytocin levels to the investigation of oxytocin sensitivity (*i.e*., genetic variation in the oxytocin receptor gene) to more invasive and experimental approaches involving stimulation designs using intranasal oxytocin administration. A majority of studies have investigated populations with anorexia nervosa.

5.1. Alterations in Oxytocin Pathways in Populations with Eating Disorders

Potential alterations in basal oxytocin functioning have predominantly been investigated in patients with anorexia nervosa, *e.g*., by assessing CSF, plasma or urinary oxytocin levels in affected and recovered individuals. Recent evidence shows an oxytocin deficiency in the acute state of anorexia nervosa ([63, 84] for review). This seems surprising at first glance, given the known anorexigenic effect of oxytocin. Of note, postprandial oxytocin levels were found to be elevated in patients with anorexia nervosa, and they have been positively related to eating disorder symptoms, anxiety and depression [84]. This pattern has led to different hypotheses on potential mechanisms behind this "paradoxical" oxytocin pattern in anorexia nervosa: low fasting oxytocin levels might represent a trait variable favoring the development of the disorder, or they might be a secondary phenomenon constituting an adaption to chronic mal- and undernutrition. Animal experiments indicate that fasting acutely suppresses excitatory synaptic input to PVN oxytocin neurons, an effect that is reversible by food intake; in contrast, prolonged fasting may lead to persistent downregulation of oxytocin neurons, thereby triggering a vicious cycle that may contribute to the pathogenesis of anorexia nervosa [85]. Further clinical data on oxytocin functioning in current and recovered patients, which could shed light on this question, are mixed. Basal plasma oxytocin concentrations were comparable between female patients with anorexia nervosa or bulimia and normal controls [86], and normal CSF oxytocin concentrations were detected in patients who had recovered from anorexia [87]. However, while basal serum oxytocin levels were likewise found to be comparable between anorectic patients and healthy controls in related experiments [88], they turned out to be reduced in fully [88] and partially recovered patients with anorexia nervosa [89]. Other studies found reduced fasting oxytocin levels in CSF [90] and plasma [91] also in women with current anorexia nervosa. It is of course to note that differences in study design and analytical methods as well as the relatively small sample sizes might contribute to such diverging findings ([92] for a preliminary meta-analysis).

Independent of this trait vs. state question, it has been suggested that oxytocin dysfunction in anorexia nervosa might be involved in a complex dysregulation of homeostatic and reward-driven signals in eating control. Oxytocin is known to also partly communicate rewarding aspects of food intake [54], and reward processing has recently been discussed as a major etiological pathway of anorexia nervosa

[93]. Oxytocin deficiency might communicate reduced satiety to homeostatic and motivational brain areas in order to counteract restrictive food intake in anorexia nervosa [88, 91]. Concerning the postprandial rise in oxytocin, it has been speculated that this might be related to anxiolytic effects of this hormone, reducing stress and anxiety during /after meal consumption, which represents an aversive situation in anorexia patients [88]. This hypothesis is supported by recent data showing oxytocin-induced reductions in salivary cortisol in patients with anorexia nervosa [94] as compared to healthy controls. The suggestion that oxytocin might be involved in processing of fear-related stimuli in anorexia nervosa is underpinned by two studies in this population showing reduced attentional bias to food and body-related stimuli after intranasal oxytocin delivery [94, 95]. Interestingly, the oxytocin-induced reduction in salivary cortisol was correlated with the oxytocin-induced reduction in attentional avoidance of food pictures [94], indicating an interaction of oxytocin with stress and anxiety associated with illness-related cues and behaviors.

Few studies have used intranasal oxytocin as an experimental challenge in populations with eating disorders. Kim and coworkers [96] have investigated – amongst others – the effects of a single dose of oxytocin on food diary-assessed calorie intake in patients with anorexia and bulimia nervosa and found decreased calorie intake over 24 hours in the bulimia group only (for findings of this study related to social cognition outcomes see 5.3.). Leppanen and coworkers found no effect of a single dose of oxytocin on laboratory-assessed smoothie intake in patients with anorexia nervosa [94]. The anorexigenic effect of intranasal oxytocin in bulimia patients is in line with findings in normal-weight and obese males (see 3.2.).

In patients with bulimia nervosa, no alterations in CSF and circulating oxytocin levels have been found [84, 86, 87, 90-92], while up to now there is to the best of our knowledge no mechanistic study on oxytocin function in patients with binge eating disorder (see also 5.2.). As binge eating disorder is mostly associated with overweight/obesity, one might speculate that oxytocin function in this subgroup shows parallels with that found in obesity [57] (see 3.2.), but this warrants further investigation.

A few studies have focused on potential (epi)genetic alterations of the oxytocinergic system in eating disorders. Kim and colleagues [97] investigated methylation of the oxytocin receptor gene in patients with anorexia nervosa as compared to controls and found predominantly higher methylation in some sites of the gene. Methylation alterations were associated with illness severity in terms of body mass index (BMI). However, it remains unclear if these epigenetic dysregulations represent a risk factor to develop the illness or are a consequence of the eating disorder. Oxytocin receptor polymorphisms, which amongst others regulate sensitivity to oxytocin, have been found to be associated with dysfunctional eating patterns in a large community cohort: the GG rs53576 genotype was associated with binge eating and purging, while the rs 2254298 AG/AA genotype was associated with lifetime restrictive eating [98]. In line with this, an earlier study has already described associations of the G allele of the rs53576 genotype and bulimia nervosa [97]. Together, these data represent a first hint that carriers of the G allele of oxytocin receptor polymorphisms might have a higher risk of developing bulimic-type eating disorders. A recent study has reported that A allele carriers of the rs53576 and the rs 2254298 genotype of the oxytocin receptor gene who had a previous anorexia nervosa showed increased disorder severity [99].

5.2. Findings Related to Attachment Behavior and Mother-Infant Interactions

In a recent study, Micali and colleagues [98] have investigated the gene × environment interactions of variations of the oxytocin receptor gene, maternal care and eating disorder behavior in a community sample of adult women. Genetic and epigenetic differences of the oxytocin receptor moderate the sensitivity to oxytocin, and specific genetic variants of the oxytocin receptor gene are associated with lower plasma levels of oxytocin and with differences in social behavior and affect. The authors [98] investigated > 3000 women from a large UK cohort who reported on maternal care received by their own mother and were interviewed for eating disorder symptoms as well as a range of lifetime eating disorder behavior. Blood samples of the participants were genotyped for two polymorphisms of the oxytocin receptor gene. It turned out that those women who were carriers of the rs2254298 AG/AA variant of the oxytocin receptor gene and had reported experiences of poor maternal care were four times more likely to also report binge eating and purging behavior. Referring to potential mechanisms of oxytocin / attachment behavior influences on eating disorders (see 4.1.), one might speculate that these carriers of the G allele might be more susceptible to early adversity and might respond with difficulties in self-regulation that include dysfunctional eating patterns. In line with this assumption, previous studies have shown that G allele carriers of this gene are more likely to show depression and emotional dysregulation in the context of early adversity [100].

While Monteleone and colleagues [91] in their recent study focused on the relationship between oxytocin levels and trait variables in patients with eating disorders, one of the trait facets investigated referred to *attachment* as a component of reward dependency. The authors investigated 23 patients with anorexia nervosa, 27 with bulimia nervosa and 19 healthy controls. Participants filled in the Temperament and Character Inventory (TCI), and plasma oxytocin levels were assessed. While in healthy women, 68% of plasma oxytocin levels were explained by self-reported attachment scores, underpinning the close link of this trait variable with oxytocin function, no such relationship was found in the patient groups. This indicates a disruption of the role of oxytocin for personality dimensions associated with social bonding and interpersonal relationships in patients with eating disorders, which might partly also contribute to difficulties in the area of social cognition (see 5.3.).

Taken together, there is surprisingly little evidence on changes in oxytocin function in attachment behavior as a trajectory for disordered eating, although attachment has been identified both as a relevant etiological factor in eating disorders and as a major domain of oxytocin effects (see 4.1.). Still, initial evidence supports the notion that the oxy-

tocin system might contribute to eating disorders and dysfunctional eating behavior by modulating attachment experiences in childhood, and also as a personality trait related to attachment later in life.

5.3. Findings Related to Social Cognition

The workgroup of Janet Treasure has examined the processing of social and emotional stimuli after administration of intranasal oxytocin in patients with anorexia nervosa and bulimia nervosa [83, 96, 101].

The group first [83] focused on the attentional processing of emotional faces in > 30 patients with anorexia nervosa versus control participants. Emotional faces displayed happiness, anger and disgust, and there were also neutral facial expressions as a control condition. In a visual probe task, participants were asked to respond as quickly as possible to a target stimulus that was preceded either by a neutral or emotional facial stimulus in the same target position on a computer screen. The hypothesis was that reactions to the probe become quicker if attention was already allocated to the probe position before (*i.e.*, because attention was drawn by the emotional face). This task was conducted twice, after intranasal oxytocin versus placebo administration. Oxytocin attenuated attention deployment to disgust expressions in both groups. Oxytocin changed the reaction pattern to angry faces from avoidance to vigilance in anorexia nervosa patients, but the opposite pattern was observed in healthy participants. The authors speculate that this differential pattern of oxytocin effects on anger processing might suggest that anorexia patients use different strategies for anger management – they might have difficulties coping with anger and might use suppression as a way of dealing with angry emotions [83].

In a subsequent study [96], the same group investigated how a single dose of intranasal oxytocin affects emotion recognition in > 60 patients with anorexia and bulimia nervosa as compared to healthy controls. In a dynamic facial morphing task, the expression of a human face gradually changed from neutral to emotional, showing either sadness, fear, anger or happiness, and participants had to indicate when they noticed emotion in the face for the first time. Intranasal oxytocin versus placebo improved emotion recognition especially for negative emotions in patients with bulimia nervosa and healthy controls, but no effect was found in patients with anorexia nervosa. Of note, effects of oxytocin on emotion recognition in anorexia nervosa were also investigated in a more recent study [101] that relied on a more traditional task, *i.e.*, the Reading the Mind in the Eyes Task that involves more complex emotions. Thirty patients with anorexia nervosa versus control participants were investigated. Again, intranasal oxytocin did not improve emotion recognition sensitivity in anorexia nervosa. However, in this study oxytocin did neither affect task performance in the healthy group, which is surprising considering earlier evidence (see 4.2.). In a second task, emotion expression was assessed while participants watched emotional film clips. The authors expected to find alterations in the expression of emotions in anorexia nervosa which should be alleviated by intranasal oxytocin; but again, no effect of the oxytocin administration was found in either group.

This pattern of findings might indicate that oxytocin function related to social cognition – at least when the hormone is administered in an experimental design – is intact in bulimia nervosa, as these patients show the same performance changes in an emotion recognition task as healthy individuals when receiving oxytocin (see also 4.3.). However, the lack of effect of intranasal oxytocin on social cognition outcomes in anorexia nervosa might point to profound disturbances in oxytocin function in this disorder – which might be connected to the changes in circulating oxytocin described in this patient population (see 5.1.) and also to the reported methylation alterations in the oxytocin receptor gene in anorexia nervosa [102]. Still, conclusions should be drawn very cautiously considering inconsistent findings and absent oxytocin effects in healthy participants [101]. As outlined above, methodological differences and comparably small sample sizes might be sources of such inconsistencies.

Taken together, three studies have used intranasal oxytocin to investigate hormonal effects on the processing of socio-emotional stimuli in anorexia and bulimia nervosa. Different tasks addressing different subcompetencies of social cognition have been used. While following oxytocin administration, anorexia nervosa patients showed differential responses – also compared to healthy females – in the attentional processing of negative emotions, they did not respond to oxytocin administration in tasks assessing emotion recognition, which might indicate that oxytocin function in anorexia nervosa is disturbed in a complex way, pertaining also to social cognition. In contrast, bulimia nervosa patients did not differ from healthy females in their response to oxytocin effects on emotion recognition.

6. OXYTOCIN AS A POTENTIAL INTERVENTION IN OVERWEIGHT AND EATING DISORDERS

6.1. Overweight and Eating Disorders

With regard to elevated body weight, the idea of the oxytocin system as a potential target of longer-term clinical interventions to normalize body weight [23, 57] has been buttressed by promising pilot studies in primates and humans. In DIO rhesus monkeys, four weeks of subcutaneous oxytocin administration decreased food intake by 27% and body weight by 3.3%, while energy expenditure increased by 14% [45]. Four daily intranasal doses of 24 IU oxytocin administered to obese subjects for eight weeks were reported to induce weight loss of around 9 kg along with a decrease in waist and hip circumference [103]. However, in this study with group sizes of around ten subjects, there were large pre-administration differences in BMI and age between the treatment and the control groups (36 *vs*. 30 kg/m^2, 29 *vs*. 41 years).

Beyond the potential of oxytocin to influence (excess) body weight, oxytocin pathways have also been suggested as innovative treatment targets for eating disorders [89, 104], inasmuch as intranasal oxytocin might represent a useful adjunctive intervention in the therapy of these disorders. However, (epi)genetic data outlined above suggest that this approach might only exert its effects in carriers of specific alleles [99]. As mentioned above, one study has reported reduced self-reported calorie intake in patients with bulimia

nervosa after a single dose of intranasal oxytocin [96]. While the evidence for an anorexigenic effect of this hormone in bulimia (and other eating disorders) clearly has to be consolidated, one might cautiously speculate that the oxytocin system could be a treatment target in bulimia nervosa – and potentially also for binge eating in general.

Intranasal oxytocin might also represent a treatment option for anorexia nervosa, potentially by unfolding anxiolytic effects or reducing dysfunctional attentional processes in relation to disorder-related processes (food intake, body image). However, it is unclear if intranasal oxytocin can positively influence disturbances in social cognition in anorexia nervosa because the three currently available studies show mixed results regarding the processing of socio-emotional information in these populations [83, 95, 101]. Kim and coworkers [83] suggested that intranasal oxytocin administration could be helpful in improving emotional processing and social communication in anorexia nervosa, especially with respect to anger-related emotions, as the authors predominantly found differential effects of oxytocin on processing of anger in this patient group. However, in two later studies on emotional recognition, oxytocin did not influence task performance in anorexia patients (see 5.3.). The evidence on anorexigenic effects of oxytocin outlined in this review moreover puts a caveat on the idea of administering oxytocin to patients with anorexia nervosa, although it remains to be seen how potential socio-emotional improvements relate to changes in eating behavior.

6.2. Sex Differences and Reward-related Mechanisms

It is to point out in this context that potential sex differences in the impact of oxytocin on eating behavior, which are suggested by some animal experiments [46], have not been addressed in humans, but obviously could be of major relevance when considering respective differences in normal and disordered eating. Also, whereas intranasal administration of oxytocin at doses from 18-40 IU was not found to induce acute side-effects [31], chronic oxytocin delivery has been associated with detrimental effects on social behavior in a number of animal studies [105-107]. Such outcomes may have their root, at least in part, in oxytocin-induced changes in reward-processing pathways, which, as outlined above, are likely to mediate some of the hypophagic effects of oxytocin in humans. Interactions between oxytocin and dopamine signaling in the regulation of pair bonding were described in animals [108], but also humans [109]. Intranasal oxytocin increases activation of the ventral tegmental area (VTA) in nulliparous and postpartum women exposed to images of crying infants as well as sexual stimuli [110], and oxytocin enhances VTA activation in response to cues that signal social reward or punishment in dependence of intra-individual differences in sociability [111]. Against this backdrop, any oxytocin-related interventions aiming to attenuate overeating and reduce body weight should pay close attention to the major role of oxytocin in attachment behavior and social cognition [112]. On the other hand, it is exactly these functions of oxytocin that may render it a promising target in emerging psychoneuroendocrine approaches to the therapy of eating disorders.

CONCLUSION AND FUTURE DIRECTIONS

There is emerging evidence for a role of oxytocin in the disease process of anorexia nervosa. This role might not only be communicated *via* homeostatic and reward-related mechanisms directly related to the regulation of food intake, but also *via* pathways involving early experiences with attachment as well as social cognition. There is a scarcity of respective studies in bulimia nervosa. Whereas evidence suggests no alterations in circulating oxytocin concentrations in this eating disorder, recent preliminary genetic evidence points to a potential genetic risk for binge eating behavior / bulimia-type eating disorders associated with variants of the oxytocin receptor gene [97, 98]. Moreover, there is preliminary evidence for a reduction in calorie intake after oxytocin administration in bulimia nervosa [96]. To the best of our knowledge, no study has yet investigated oxytocin function in binge eating disorder. This fact comes as a surprise considering first evidence for a distinct hypophagic effect of oxytocin in subjects with obesity, which is commonly associated with binge eating behaviour. Since experiments in humans on the metabolic effects of oxytocin in general are still rare, well-controlled and larger trials are needed to investigate the potential of oxytocin in the treatment of eating- and weight-related disorders. At the time of writing, around 15 investigations into the effects of oxytocin in overweight subjects were listed on clinicaltrials.gov, the majority of which focus on Prader-Willi syndrome. In contrast, interventional clinical trials on oxytocin effects on anorexia nervosa, binge eating disorder or bulimia nervosa have yet to be announced. The currently available results strongly suggest that such studies may expand an important future field of research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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