Oxytocin therapy in hypopituitarism: challenges and opportunities

Running title: Oxytocin in hypopituitarism

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Summary: Patients with hypopituitarism display impaired quality of life and excess morbidity and mortality, despite apparently optimal pituitary hormone replacement. Oxytocin is a neuropeptide synthesised in the anterior hypothalamus which plays an important role in controlling social and emotional behaviour, body weight and metabolism. Recent studies have suggested that a deficiency of oxytocin may be evident in patients with hypopituitarism and craniopharyngioma, and that this may be associated with deficits in cognitive empathy. Preliminary data hint at potential benefits of oxytocin therapy in improving these deficits and the accompanying metabolic disturbances that are common in these conditions. However, several challenges remain, including an incomplete understanding of the regulation and mechanisms of action of oxytocin, difficulties in accurately measuring oxytocin levels and in establishing a diagnosis of oxytocin deficiency, and a need to determine both the optimal mode of administration for oxytocin therapy and an acceptable safety profile with long-term use. This review considers the data linking oxytocin to the neuropsychological and metabolic disturbances evident in patients with craniopharyngioma and hypopituitarism, and describes the challenges that need to be overcome before replacement therapy can be considered as a therapeutic option in clinical practice.

Synthesis and Secretion

First discovered by Sir Henry Dale in 1906 and sequenced by du Vigneaud and colleagues in 1954, oxytocin (OT) is a nonapeptide hormone synthesised principally by magnocellular neurons located in the hypothalamic paraventricular and supraoptic nuclei (figure 1). OT is initially synthesised as an inactive precursor protein containing its carrier protein neurophysin I, which undergoes progressive hydrolysis to release active OT. A single axon arising from each magnocellular neuron projects to the posterior pituitary gland where OT release is triggered by exocytosis from neurosecretory vesicles in response to depolarisation (1). The blood-brain barrier largely prevents OT molecules released in this manner from re-entering the central nervous system (2). Nevertheless, endogenous brain OT concentrations are significantly higher than in the periphery (1) and do not appear to correlate with plasma levels (3). OT is also released to other brain regions via dendritic diffusion as well as via axonal connections from parvocellular neurons to regions such as the nucleus accumbens, nucleus tractus solitarius, arcuate nucleus and spinal cord (figure 1). Furthermore, OT is synthesised at other sites, including the retina, pancreas, thymus, adrenal medulla, placenta and corpus luteum, although the physiological relevance of production at these sites is unclear.

Early studies suggested that circulating plasma OT concentrations are relatively stable in the basal state (4) but recent observations using deconvolution analysis have confirmed that a pulsatile pattern of OT secretion exists in men at rest and that OT concentrations correlate with indices of socio-emotional functioning (5). In keeping with the progressive rise in OT levels during pregnancy, OT concentrations are stimulated in response to oestrogen administration (6, 7); however, they may not vary significantly according to phase of the menstrual cycle (6, 7). Some

(4, 8), but not all (9), studies report a diurnal variation in secretion, with concentrations at their lowest in the afternoon and evening, and rising steeply after midnight (4). It is unclear if ageing has an effect on secretion: although one study showed no effect of age on either the pattern of release or absolute OT concentrations (4), only a small number of subjects were included and further studies are needed. In women, physiological stimuli such as breastfeeding and labour induce a pulsatile release of OT into the peripheral circulation whereas in men, peripheral OT concentrations have been shown to rise during sexual arousal (10).

Peripherally administered OT has a very short half-life in human plasma (2-8 minutes) (11) and displays poor permeability across the blood-brain barrier, with <1% of peripherally-administered OT appearing in the cerebrospinal fluid (CSF) (2, 12). These pharmacokinetic properties present a challenge when considering its therapeutic potential as a neuroactive drug. OT exerts its effects through binding to the G protein-coupled OT receptor. Although only one canonical receptor for OT is thought to exist in mammals, arginine-vasopressin (AVP), which shares seven of nine amino acids, is thought to have three: the V1a, V1b and V2 receptors. These evolutionarily ancient receptors exhibit a high degree of structural homology, hence it is not surprising that considerable cross-talk between OT and AVP and their receptors can occur (13). This has implications not only for our understanding of the roles of these peptides in a variety of physiological processes but also for drug design with respect to receptor selectivity.

Physiological effects

OT has a well-established role in the regulation of labour, in keeping with its derivation from the Greek for ‘quick birth’. It stimulates cervical ripening and dilatation, is uterotonic, and facilitates

uterine contraction and clotting in the postpartum period. OT also stimulates breast myoepithelial cells to help initiate the let-down reflex in lactation (figure 2).

More recently, its role in the regulation of a number of other physiological processes has become appreciated, notably in relation to food intake and metabolism (14). Knockout mice deficient in either OT or the OT receptor are obese and glucose intolerant (15, 16), whilst OT administration reduces food intake, increases energy expenditure and improves glucose homeostasis (17-19). The effects on food intake are rapid and sustained (17, 18), with obese rats appearing to be more sensitive to the effects of OT on weight loss than lean animals (20). In humans, studies have shown that peripheral OT levels are elevated in obesity (21) and the metabolic syndrome (22), and correlate with BMI and fat mass (21, 22). Conversely, OT concentrations may be lowered in the presence of overt diabetes (23-25). Acutely, intranasal OT administration reduces caloric intake (26, 27) with a preferential reduction in fat consumption (26); as in animals, these effects are more pronounced in obesity (27). These actions may be mediated at least in part by modification of hedonic as well as homeostatic pathways (14, 17, 28). Single dose experiments have also shown an increase in fat oxidation (26), and beneficial effects on glucose homeostasis and insulin sensitivity (26-29). Conversely, the benefits seen in animal models with respect to increased energy expenditure have not yet been confirmed in humans (26, 28). An important caveat is that the OT dose used in these studies may be considered supra-physiological (24 IU), exceeding both the estimated OT store in the posterior pituitary (14 IU) and the intravenous doses employed in labour (1-30 mIU/min). At these doses, some of the effects of OT may be mediated via actions at AVP receptors (30). Furthermore, studies to date have been largely limited to men, hence it is unclear whether these metabolic benefits are also apparent in women. In contrast to acute administration, only a few studies have examined the effects of sustained OT administration on

body weight and metabolic outcomes, although a number of clinical trials are ongoing. In a randomised, placebo-controlled study of intranasal OT (24 IU four times daily) in subjects with overweight/obesity, OT reduced body weight by a mean of 9kg after 8 weeks, albeit that only 9 participants received active treatment (19). Conversely, no effects on weight were seen in two randomised, placebo-controlled trials of intransal OT in Prader-Willi syndrome (31, 32), although the total daily OT exposure was lower in these studies than in Zhang *et al* (19).

Oxytocin receptors are expressed in the adrenal and anterior pituitary glands, hence it is not surprising that OT administration has an effect on the hypothalamic-pituitary-adrenal (HPA) axis. Studies have shown consistently that OT, whether administered intravenously or intranasally, reduces ACTH and cortisol secretion under both basal and stress conditions (33-35). Intravenous OT has also been shown to block corticotrophin-induced ACTH release (36), although no reports of hypoadrenalism have emerged to date. In animals, OT has been shown to modulate sodium balance but recent data in humans showed no influence of dietary sodium intake on circulating OT levels (37). Nevertheless, given its ability to bind to vasopressin receptors including the V2 subtype, hyponatraemia may develop in response to treatment, at least in high doses such as those used in labour (38).

Psychological Effects

Early studies in the 1990s demonstrated profound effects of OT on sexual and maternal behaviour in animals, since replicated in human studies which confirm an important role of OT in normal parenting (39). OT is now known to exert a wide range of effects on human social and emotional behaviour (figure 2), from influencing the way in which individuals respond to social exclusion

(40, 41), to moral dilemmas (42) and how they allocate resources (43). Moreover, OT regulates the way in which individuals process emotional information (44) and, in turn, facilitates the identification of emotions (45); as such OT may be implicated in many mental health disorders. Altered OT concentrations or responses are evident in patients with postnatal depression (46), schizophrenia (47), autism spectrum disorder (ASD) (48) and attention-deficit hyperactivity disorder (49).

Given OT's pivotal role in adaptive social behaviour, studies have investigated the potential therapeutic role of OT administration in improving characteristic behavioural symptoms associated with these disorders. For example, Tauber *et al* (50) found that infants with Prader-Willi Syndrome who received intranasal OT showed improved sucking, increased acylated ghrelin production and improved parent-infant interaction. To date, the disorder that has received the most attention with regard to the therapeutic potential of OT is ASD, with a systematic review finding significant benefits with respect to emotion recognition and eye-gaze (48). While clinical trials into the effects of OT in individuals with ASD are ongoing, larger and longer-term studies are needed to confirm these findings and those in other mental health disorders.

Morbidity, mortality and quality of life in hypopituitarism: an unmet need

Hypopituitarism, referring to reduced secretion of pituitary hormones, affects roughly 45 people per 100,000 of the general population. Pituitary adenomas, extrasellar tumours and treatments for these tumours (surgery, radiotherapy) account for the majority of cases in adults, although infective, inflammatory, infiltrative, traumatic, vascular and congenital disease may also occur. This diverse range of aetiologies contributes to differences in morbidity and treatment outcomes.

Notably, hypothalamic insult, whether arising directly from tumours (such as craniopharyngioma) or treatments for such tumours (especially surgery), is a major cause of morbidity (51, 52), not least due to obesity and its metabolic sequelae, arising as a result of disruption to appetite-regulating centres. Although the introduction of glucocorticoid, thyroid, sex steroid and growth hormone replacement therapy has transformed outcomes in hypopituitarism, a number of studies have shown that the mortality and morbidity experience of patients still does not reach population norms. Meta-analyses have consistently demonstrated an excess mortality in hypopituitarism despite apparent optimal replacement therapy (53, 54), driven largely by deaths related to vascular disease. The risks of premature death appear greater in young-onset disease and in women (54). Of note, the standardised mortality ratio in patients with craniopharyngioma is particularly high (52, 54, 55).

Several studies have demonstrated impaired quality of life (QOL) in patients with hypopituitarism, whether measured by generic or disease-specific tools (56, 57). QOL is particularly impaired in craniopharyngioma (58, 59), with the most common domains affected including emotional and social functioning (58, 59). Additional treatments are therefore needed to address this burden and to improve patient experience.

Oxytocin in hypopituitarism

In light of the impaired QOL, neuropsychological deficits and obesity frequently evident in patients with craniopharyngioma, and OT's synthesis in the hypothalamus, studies have begun to address whether OT deficiency is present in hypopituitarism, and if so whether this is accompanied by psychological deficits that might be amenable to therapeutic intervention (table 1). A 2016 case

report highlighted an improvement in pro-social behaviour in response to nasal OT in a boy following surgical treatment of a craniopharygioma (60). Daubenbüchel and colleagues subsequently compared salivary OT concentrations in 34 patients in the German Childhood Craniopharyngioma Registry and 73 healthy volunteers (61), finding no difference in OT levels between groups. They speculated that this might reflect either preserved hypothalamic function or compensatory secretion by other neuronal pathways, such as the medial preoptic area, striaterminalis and lateral amygdala (62). Dendritic as opposed to axonal OT release might also account for these findings. However, they did find lower fasting OT concentrations in patients with post-surgical lesions to the anterior hypothalamus (where the paraventricular and supraoptic nuclei are located), albeit that only 6 patients fell into this category. Counter to expectation, OT levels were not lowered in patients with more extensive hypothalamic involvement (anterior and posterior regions), for reasons that aren't immediately clear. Gebert and colleagues subsequently compared salivary OT levels, at baseline and following an exercise stimulus, in 26 adult craniopharyngioma patients and 26 age/sex-matched controls (63). OT concentrations as a whole were not different between groups, but were reduced in patients with hypothalamic damage as assessed by MRI. Exercise-induced rises in OT were also blunted in the patient group. Of note, they did not find a relationship between the presence of diabetes insipidus and OT concentrations, indicating that diabetes insipidus cannot be used reliably as a proxy for OT deficiency, with the caveat that desmopressin may cross-react in some immunoassays. Counter to expectation, higher baseline OT concentrations were associated with higher trait anxiety, whereas blunted OT secretion in response to exercise was linked with higher state anxiety. No association was observed with measures of empathy. Our own study examined salivary OT concentrations in fifty-five participants, comprising 20 patients with central diabetes insipidus and anterior hypopituitarism,

15 patients with anterior hypopituitarism alone (clinical controls) and 20 healthy volunteers (64). Groups were matched for age and gender. To our surprise, hypopituitarism was associated with reduced OT concentrations irrespective of the presence or absence of diabetes insipidus, potentially indicating an influence of anterior pituitary hormones on OT secretion. Patients with hypopituitarism also performed worse on two empathy tasks, with regression analyses revealing that OT concentrations significantly predicted ability to correctly identify facial expression. A specific deficit in empathy was also supported by analysis of self-report measures, with hypopituitary patients demonstrating significantly lower trait empathy compared to healthy controls. In a recent small pilot study in 10 childhood craniopharyngioma patients, Hoffman and colleagues demonstrated an improvement in emotion recognition in response to a single intransal dose (24 IU) of OT (65). Collectively, these data suggest that patients with hypopituitarism may present with a deficiency in OT associated with reduced cognitive empathy, and that this might be amenable to treatment with OT replacement.

In contrast to neuropsychological studies, observations on the effects of OT on body weight in patients with hypopituitarism are sparse, and limited to a single case report in which a 13 year old boy with hypothalamic obesity post-surgical resection of a craniopharyngioma was treated with OT (66). MRI had shown evidence of injury to the anterior hypothalamus. OT was administered intranasally for 10 weeks at an eventual dose of 6 IU daily. In addition to weight loss of 4.4 kg during this time, qualitative improvements with respect to satiety, reduced urgency to eat and decreased food preoccupation were noted. Subsequent addition of the opiate antagonist naltrexone in combination with OT resulted in continued profound reduction in weight and hyperphagia. Although testosterone therapy to induce puberty may have contributed in part to these improvements, it should be noted that this was not introduced until 4 months after OT

commencement. OT treatment was well-tolerated with no reported adverse effects. Finally, several patient reports on blog and social media sites describe positive benefits in response to OT therapy used off label. Whilst such anecdotes should be treated with some caution, they should at least serve as a reminder that the demand for new treatments to improve quality of life is high in the hypopituitary community.

Diagnostic challenges

Whilst these observations of a potential neuropsychological and metabolic benefit of OT in hypopituitarism are encouraging, a number of challenges need to be addressed before OT can be considered for adoption into clinical practice. Firstly, reliable measurement of plasma OT concentration is not straightforward (67). Falsely elevated OT levels are often observed with modern radioimmunoassays due to interference from other immunoreactive products (68), a problem common also to enzyme-linked immunosorbent assays (ELISAs). Sample extraction (by solid phase or solvent) is a procedure designed to eliminate the effect of potentially interfering products, reduce matrix effects and concentrate the analyte from the sample before analysis. Whilst extraction removes some of these interfering substances, ELISAs may still detect OT degradation products, whose biological activity is unknown. Moreover, the need for an extraction step is itself open to question since it eliminates protein-bound OT with the potential to falsely lower OT concentrations (69). Mass spectrometry-based methods may offer an important advance as they offer high selectivity and sensitivity. OT concentrations measured in this manner are significantly higher than reported for established techniques since total OT is measured, which is largely protein-bound (69). Salivary OT measurement is also problematic and requires further validation,

not least because of weak correlation with immunoassay measures of unextracted OT in plasma (67); the biological relevance of OT measured at this site is also unclear. Furthermore, since the regulation of peripheral and central OT secretion might be mediated independently of one another (70), peripheral measurement may not necessarily reflect central activity.

A second challenge lies in the confirmation of a diagnosis of OT deficiency, since the physiological mechanisms involved in OT regulation are still not fully understood. Akin to the demonstration of ACTH or GH deficiency in patients with hypopituitarism, a stimulation test might be required to completely unmask OT deficiency (63). The optimal method by which this can be confirmed reproducibly needs to be established, whilst studies have already suggested that the presence of central diabetes insipidus is not a reliable enough surrogate (63).

Therapeutic challenges

A number of therapeutic challenges also need to be overcome before OT can be considered as a viable treatment option in hypopituitarism. These include its short half-life, optimal mode of administration and the safety profile of chronic administration. OT is currently administered as an intravenous preparation to induce or augment labour, and used intramuscularly or intravenously in the prevention and treatment of postpartum haemorrhage. Neither of these modes of delivery are viable as a long-term treatment option, not least because of the very short half-life of OT (11). Intranasal OT is an unlicensed but commercially available preparation which in supra-physiological doses appears to cross the blood-brain barrier (71). This suggests that intranasal OT might exert its actions, at least in part, through central as well as peripheral pathways. However, the typical dosing frequency of six sprays four times daily (24 IU) is inconvenient. Furthermore,

it is unclear whether the observation made in mice of greater efficacy with respect to weight loss in response to continuous as opposed to bolus OT delivery (72) carries the same physiological importance in humans. Despite these limitations, intranasal OT has been used widely in human research studies with largely reassuring safety data to date, at least in the acute setting. In the 1960s-1970s intranasal OT was used clinically as an alternative to intravenous OT in the induction and maintenance of labour. A study of over 1800 women treated in pregnancy showed a low rate of adverse events (73). There are fewer safety data with respect to chronic administration, although a recent systematic review of adverse events following long-term application (>5 weeks) in patients with ASD gave further reassurance (74). The most common adverse events were nasal discomfort, tiredeness, irritability, diarrhoea and skin irritation but the frequency of these did not differ from placebo. Chronic intranasal OT administration has also been shown to be safe in other patient groups (19, 31, 32). Nevertheless, observations from OT use in pregnancy indicate that headache and nausea are the most common side-effects that limit tolerability, whilst cardiovascular events (arrhythmias, blood pressure fluctuation) and hyponatraemia may cause particular clinical concern. These may be mediated in part via off-target actions at AVP receptors. Moreover, the actions of OT in down-regulating activity of the hypothalamic-pituitary-adrenal axis (33-36) require particular attention when considering OT for use in hypopituitarism.

Longer-acting OT analogues may circumvent some of these therapeutic challenges, notably with respect to extended half-lives leading to reduced frequency of administration. Carbetocin, [Ser4, Ile8]-oxytocin and [Asu1,6]-oxytocin are three such examples which have been shown to reduce weight and improve glucose regulation in obese diabetic mice (19, 75). However, human data are currently lacking.

Conclusions

Whilst a number of studies have suggested that hypopituitarism may be associated with OT deficiency, and that OT administration has the potential to improve neuropsychological outcomes, a number of challenges remain. A better understanding of the physiological regulation, interplay with other endocrine axes and mechanisms of action of OT is critical, as are improvements in measurement techniques, in order to understand if hypothalamic disease and hypopituitarism are truly associated with OT deficiency or not. Further studies are also needed to confirm an association of any deficiency in OT secretion with adverse psychological and metabolic outcomes. Interventional studies are subsequently needed to clarify which dose, mode and frequency of OT administration is associated with the best clinical outcomes, whilst long-term trials will need to demonstrate an acceptable safety profile. Despite these many challenges, recent observations have highlighted the OT axis as worthy of further study in patients with craniopharyngioma and hypopituitarism, and suggest that OT replacement might have the potential to improve clinical outcomes in patients with these conditions.

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Legends for figures.

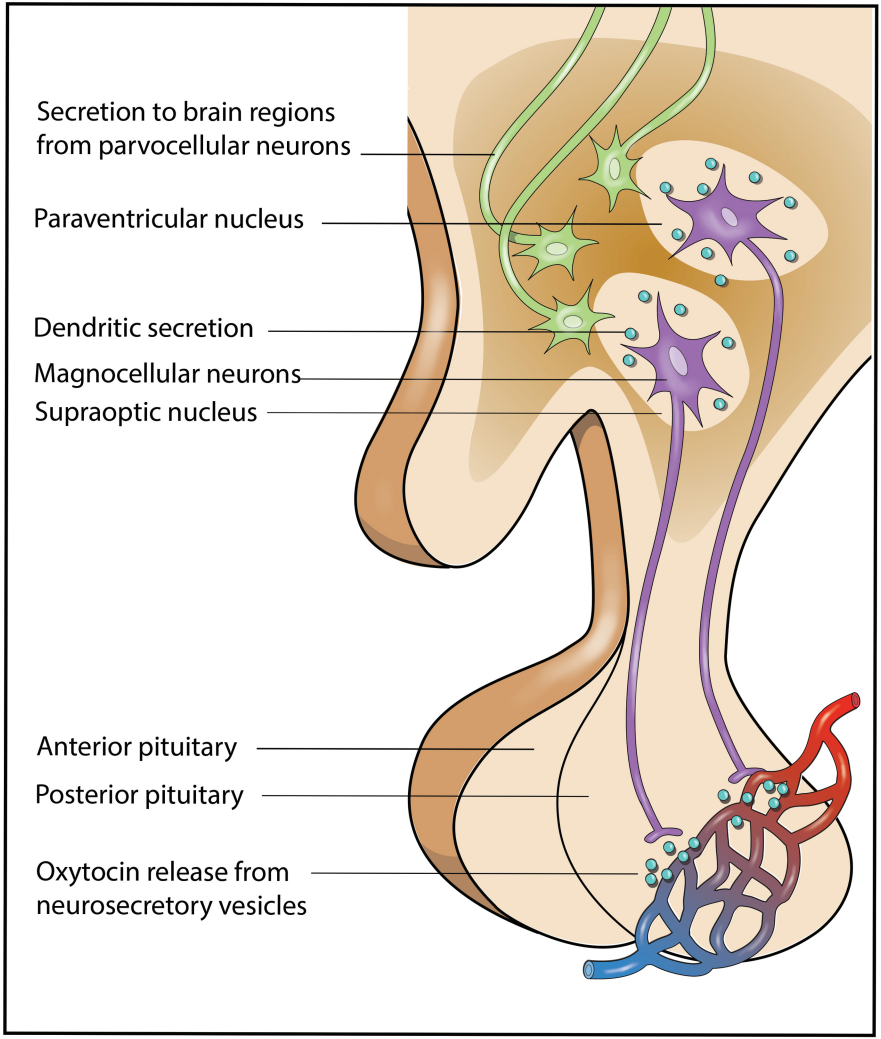
Figure 1. Oxytocin synthesis and secretion

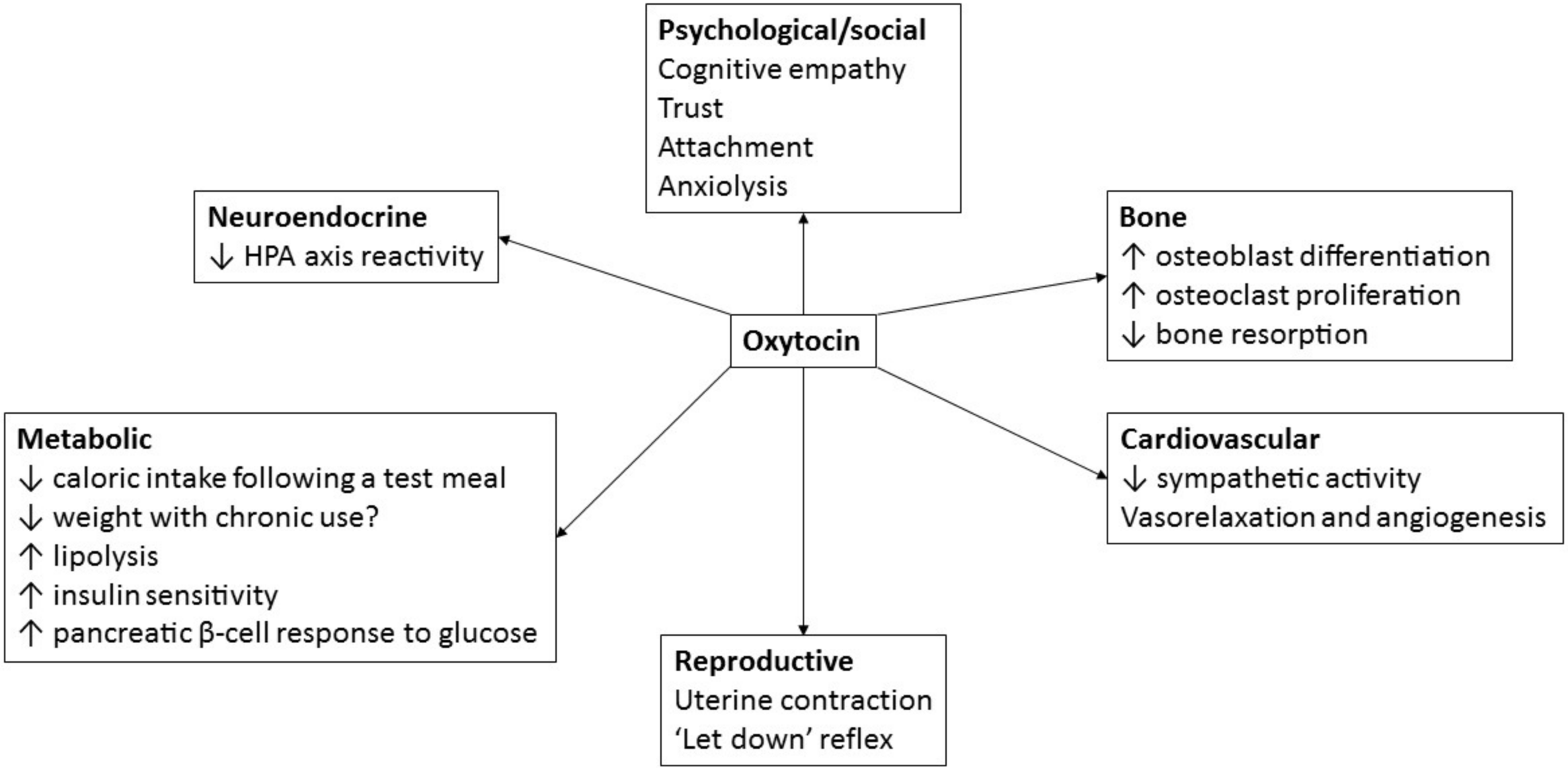
Figure 2. Actions of oxytocin

Table 1. Clinical studies of OT in craniopharyngioma and hypopituitarism.

Study	Design	Participants	Measures	Oxytocin measurement	Key findings
Daubenbüchel *et al* (61)	Case-control	34 CP patients. 73 healthy volunteers.	Baseline and stimulated (post-meal) OT concentrations. Associations with anthropometric and radiological parameters	Saliva. Enzyme immunoassay after extraction.	Reduced OT concentrations in patients with anterior hypothalamic surgical lesions. Change in OT after meal in CP patients correlated with BMI.
Gebert *et al* (63)	Case-control	26 CP patients. 26 healthy controls	Baseline and stimulated (post-exercise) OT concentrations. Empathy, depression and anxiety scores.	Saliva. Radioimmunoassay after extraction.	Blunted OT release post-exercise in CP. Higher baseline OT associated with higher trait anxiety. Blunted OT release linked with higher state anxiety. CDI not a reliable surrogate for OT deficiency
Daughters *et al* (64)	Case-control	20 patients with CDI and AP. 15 patients with AP alone. 20 healthy controls.	Baseline OT concentrations. Empathy tasks (Reading the mind in the eyes; facial emotion recognition). Personality measures.	Saliva. Enzyme immunoassay after extraction.	Reduced OT concentrations in AP irrespective of CDI. Impaired empathic ability in patients with AP.
Hoffmann *et al* (65)	Acute intranasal OT administration	10 CP patients.	OT concentrations before and after intranasal OT administration. Emotion recognition (Geneva multimodal emotion portrayals corpus; Multidimensional mood questionnaire)	Saliva and urine. Radioimmunoassay after extraction.	Improved emotion identification in patients with post-surgical lesions in the anterior hypothalamus.
Cook *et al* (60)	Case report	Child with CP	Parent-observed behaviour in response to intranasal OT.	Not measured	Increased desire for socialisation. Improved affection towards family.
Hsu *et al* (66)	Case report	Boy with CP	BMI and parent-observed behaviour with respect to food intake in response to chronic intranasal OT alone or in combination with naltrexone.	Not measured	Reduction in weight and BMI z-score. Improved satiety, reduced urgency to eat and decreased food preoccupation.

CP Craniopharyngioma. CDI Central diabetes insipidus. AP Anterior hypopituitarism. BMI Body mass index.


Secretion to brain regions
from parvocellular neurons
Paraventricular nucleus
Dendritic secretion
Magnocellular neurons
Supraoptic nucleus
Anterior pituitary
Posterior pituitary
Oxytocin release from
neurosecretory vesicles


Psychological/social
Cognitive empathy
Trust
Attachment
Anxiolysis
Neuroendocrine
↓ HPA axis reactivity
Bone
↑ osteoblast differentiation
↑ osteoclast proliferation
↓ bone resorption
Oxytocin
Metabolic
↓ caloric intake following a test meal
↓ weight with chronic use?
↑ lipolysis
↑ insulin sensitivity
↑ pancreatic β-cell response to glucose
Cardiovascular
↓ sympathetic activity
Vasorelaxation and angiogenesis
Reproductive
Uterine contraction
'Let down' reflex