BioMol Concepts, Vol. 1 (2010), pp. 367–380 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/BMC.2010.036

Review

Oxytocin: recent developments

Nicole C. Tom and Stephen J. Assinder*

Discipline of Physiology, School of Medical Sciences and Bosch Institute, University of Sydney, Sydney 2006, NSW, Australia

*Corresponding author
e-mail: stephen.assinder@sydney.edu.au

Abstract

Oxytocin is a neurohypophyseal hormone that is produced centrally by neurons in the paraventricular nucleus and supraoptic nucleus of the hypothalamus. It is released directly into higher brain centres and into the peripheral circulation where it produces a multitude of effects. Classically, oxytocin is known for inducing uterine contractions at parturition and milk ejection during suckling. Oxytocin also acts in a species and gender specific manner as an important neuromodulator. It can affect behaviours associated with stress and anxiety, as well social behaviours including sexual and relationship behaviours, and maternal care. Additionally, oxytocin has been shown to have a variety of physiological roles in peripheral tissues, many of which appear to be modulated largely by locally produced oxytocin, dispelling the notion that oxytocin is a purely neurohypophyseal hormone. Oxytocin levels are altered in several diseases and the use of oxytocin or its antagonists have been identified as a possible clinical intervention in the treatment of mood disorders and pain conditions, some cancers, benign prostatic disease and osteoporosis. Indeed, oxytocin has already been successful in clinical trials to treat autism and schizophrenia. This review will report briefly on the known functions of oxytocin, it will discuss in depth the data from recent clinical trials and highlight future targets for oxytocinergic modulation.

Keywords: behaviour; cancer; oxytocin; oxytocin receptor.

Introduction

Oxytocin was named for its ability to induce uterine contractions (1) and was the first peptide to be synthesised in its biologically active form (2). Oxytocin is mainly produced by the magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus, and is released directly into higher brain regions or into the blood stream via projections that extend to the neurohypophysis (1). In the rat, oxytocin neurons are known to project into the central, anterior, basal and lateral amygdala, substantia nigra, nucleus tractus solitaris, nucleus motoris dorsalis vagus, nucleus reticularis lateralis and into the spinal cord (3). Within the medulla, PVN neurons project to the dorsal motor nucleus of the vagus, commissural nucleus and the lateral reticular nucleus (3). More recently, oxytocin synthesis has been observed in several tissues (1), e.g., the atria of the heart (4), prostate gland (5) and epididymis (6).

Oxytocin is a nonapeptide that is structurally and functionally related to vasopressin and, owing to a high degree of contiguity, both peptides share partially overlapping functions and define larger classes of neurohypophyseal peptides that share a high degree of homology (1). Classification into either vasopressin or oxytocin class of hormones is dependent on the amino acid present at position 8, with a neutral amino acid defining oxytocin class and a basic amino acid defining vasopressin class (1).

The oxytocin gene is highly conserved between species and shares a common locus with the vasopressin gene. Oxytocin lies on the positive strand, whereas vasopressin lies on the negative strand. Hence, transcription of both genes occurs in opposite directions (7). In humans, oxytocin is transcribed from a single copy gene on chromosome 20p13 comprising three exons and four interposing introns (7) (Figure 1A). The resulting translated 12.8-kDa nonapeptide forms a disulphide bridge between cysteine residues resulting in a six amino acid cyclic peptide with a three amino acid carboxyl tail (2) (Figure 1B).

The physiological regulation of the oxytocin gene remains elusive. There is evidence for tissue specific endocrine regulation as the *OXTR* promoter contains binding sequences for oestrogen (8), retinoic acid (9) and thyroid hormone receptors (10) that overlap in a region referred to as a multihormone response element. Oxytocin is upregulated by oestrogen in the PVN and the uterus (11). Oestrogen induced upregulation of uterine oxytocin is blocked by progesterone, whereas in the PVN it is blocked by the thyroid hormone (11, 12).

Oxytocin exerts its biological effects by binding and activating the oxytocin receptor. The oxytocin receptor is a typical G-protein-coupled receptor containing seven transmembrane domains and is transcribed from a single copy gene on chromosome 3p25 in humans (13). The receptor is widely expressed in mammalian organs including the brain, heart, epididymis, prostate, testis, uterus (1) and bone reflecting the pleotropic effects of oxytocin. The oxytocin receptor is unique in its ability to be rapidly upregulated and downregulated in response to stimuli including parturition (13) and, similar to the oxytocin gene, is under the transcriptional control of oestrogen (14).

Activation of the oxytocin receptor results in several responses which are G protein and cell type dependent. Cou-

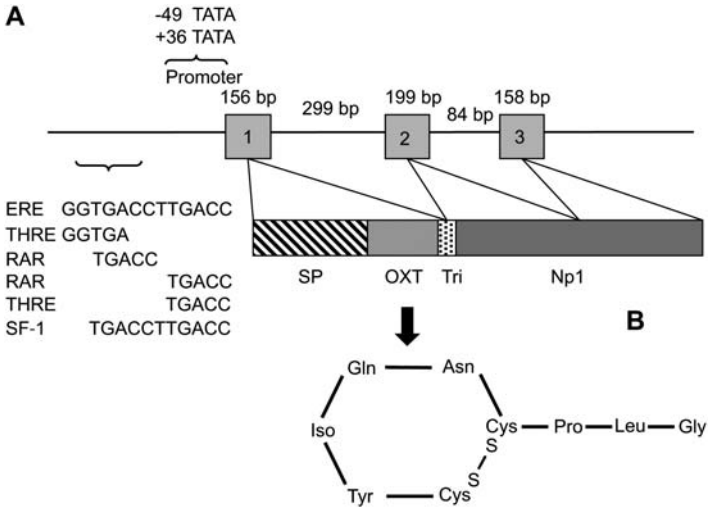

Figure 1 Schematic diagram showing the structure of the human oxytocin gene, mRNA and protein.
(A) The oxytocin gene comprises three exons (numbered boxes) and four introns (line). The composite hormone response element (CHRE) and other conserved regions of hormone responsiveness are given with relative positions of promoter elements upstream (-) and downstream (+) of the transcript start site. Retinoic acid response elements (RARs) and thyroid hormone response elements (THREs) are shown, as is the full oestrogen response element (ERE) spanning the CHRE. Additional TGACC elements at -103 and -83 are able to produce a small oestrogen-mediated induction of the oxytocin promoter but these elements do not act synergistically with the ERE. The mRNA transcript is given identifying those exonic regions that encode the secretory signal peptide, oxytocin and oxytocin associated neurophysin (Np1) interspaced with a tripeptide linker. (B) Primary protein structure gives the amino acid number relative to the first cysteine. Cyclisation of the first six amino acids occurs through disulphide bond formation (s-s) between cysteines 1 and 6.

pling of the oxytocin receptor to $G\alpha_{q/11}$ initiates a phospholipase C (PLC) dependent mechanism which induces the release of calcium from intracellular stores. Increased intracellular calcium can alter neuronal excitability and trigger neurotransmitter release in neurons or cause smooth muscle contraction (1) (Figure 2). In addition to the calcium dependent pathway, the oxytocin receptor can stimulate calcium independent pathways including RhoA and ERK dependent pathways. RhoA/Rho-kinase is activated by oxytocin resulting in phosphorylation of myosin-binding subunit of myosin phosphatase and contraction of uterine smooth muscle cells (15). RhoA signalling is thought to be an important contributor to smooth muscle cell contraction as RhoA is markedly raised during pregnancy (15). Additionally, oxytocin signalling can induce phosphorylation of ERK1/2 and ERK5 which can alter gene transcription and induce contraction in smooth muscle cells by increasing prostaglandin synthesis (16, 17).

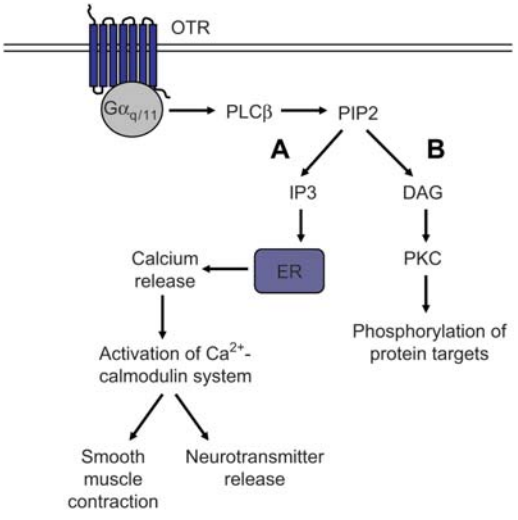

Figure 2 Classical signalling pathways of oxytocin receptor activation.
Coupling of the oxytocin receptor to $G\alpha_{q/11}$ activates a signalling cascade via phospholipase C-β (PLCβ), phosphatidylinositol-4,5-bisphosphate (PIP2). This leads to the generation of diacylglycerol (DAG) and IP3. IP3 induces release of calcium from the endoplasmic reticulum (ER) and activation of the calcium calmodulin system. This results in smooth muscle contraction or neurotransmitter release in neurons. DAG causes activation of protein kinase C (PKC) and induces the MAP-kinase pathway resulting in phosphorylation of downstream targets such as ERK1/2.

Classical actions of oxytocin

Oxytocin was first recognised for its roles in female physiology including the induction of labour and milk ejection, roles that are evidenced by increasing oxytocin levels during lactation and labour (18). Additionally, oxytocin is the strongest uterogenic substance known to man and its agonists and antagonists have been used clinically to induce labour or halt premature labour, respectively (1).

During parturition, circulating oxytocin levels rise dramatically owing to increased secretion from oxytocin neurons. Increased secretion from oxytocin neurons is

engendered by a reduction in progesterone which causes activation of SON neurons (19) and is augmented by cervical and uterine stimulation (1, 20). Moreover, the uterus becomes more sensitive to oxytocin with a rapid increase in oxytocin receptor expression that is induced by oestrogen (14). Oestrogen induced oxytocin receptor upregulation can only occur following a reduction in progesterone secretion (14). However, the role of oxytocin in parturition has been questioned as oxytocin null mice undergo parturition normally (21). The administration of oxytocin antagonists during labour in mice have demonstrated that, although oxytocin does not induce labour, oxytocin affects labour progression and the timing of birth of pups subsequent to the first (22). Its role in birthing of subsequent pups is highlighted by the heightened levels of oxytocin that are seen following the birth of the first pup (22). The lack of major effects seen in the oxytocin null mouse model could be owing to compensation by vasopressin and other stimuli that increase prostaglandin synthesis, a final event in oxytocin-induced contraction of uterine smooth muscle (20).

Oxytocin is secreted in response to suckling as part of a reflex. Suckling stimulates tactile receptors in the nipple which sends signals via the spinal cord into the PVN of the hypothalamus. Oxytocin is released in a pulsatile manner and induces contraction of the myoepithelial cells surrounding alveoli of the secretory lobes and surrounding the lactiferous ducts, promoting milk ejection (1). Oxytocin deficient mice have illustrated the importance of oxytocin in the milk ejection reflex with pups dying soon after birth due to malnourishment despite normal maternal and suckling behaviours and milk production (21).

Non-classical actions of oxytocins

Social behaviour

The relationship of oxytocin to social behaviour has been most frequently studied in the genus *Microtus* (voles) which show marked variations in social structure. Prairie voles form long-term monogamous relationships and are constantly observed to associate with their mates, produce a larger number of ultrasonic calls and secrete glucocorticoids in response to social isolation (23). Alternatively, montane voles live in isolated burrows and show little affiliation, except following parturition (23). Oxytocin receptor distribution in the brains of both species are different, presumably reflecting differences in social organisation. Prairie voles display the highest oxytocin receptor density in the prelimbic cortex, bed nucleus of stria terminalis, nucleus accumbens, midline nuclei of thalamus and lateral aspects of the amygdala. Conversely, the highest oxytocin receptor density in the montane vole is in the lateral septum, ventromedial nucleus of the hypothalamus and cortical nucleus of the amygdala (23). A similar pattern is found in singing mice *sp*. that show differences in social affiliation (24). The roles of oxytocin in social behaviour are supported by the observations that follow chronic administration of oxytocin, rats spend an increased amount of time engaging in non-sexual social behaviours such as sniffing and grooming (25). Furthermore, in oxytocin null mice pervasive social deficits are observed such as a reduction in vocalisations following removal from the nest and increased aggression (26). It is worth noting here that increased vocalisation of an unusual pattern has been reported in a mouse model of autism (27), a social disorder in which oxytocin is implicated (see below).

Such evidence from animal studies identified oxytocin as a potential treatment for social dysfunction arising from autism, schizophrenia and mood disorders. Within the past 10 years, the effect of oxytocin on affiliative behaviour in humans has been investigated in clinical trials (Table 1), the results of which are suggestive of oxytocin modulating social attachment. Oxytocin administration has been found to induce prosocial behaviours such as trust (28, 29) and can increase eye gazing, a behaviour that is necessary for identifying subtle social cues (30). Indeed, in a double-blind randomised control study in young healthy males, intranasal oxytocin could improve their ability to recognise the mood of people in the ''seeing the eyes in the mind test'' where people were asked to assign a mood based on a photograph of only a subject's eyes (31). Oxytocin has also been found to be important in regulating social memory in humans and can improve the ability of people to identify unfamiliar others from a single sighting (32). Additionally, oxytocin administration can compensate for a lack of social contact and contribute towards general health and well-being (32). Oxytocin has also been shown to improve positive communication during couple conflict (33).

Sexual behaviour

In both males and females, oxytocin is important in inducing sexual behaviour, arousal and orgasm. All behaviours are centrally mediated in a region-dependent manner.

In male rats, oxytocin injected into the hippocampus can elicit erection (34). The ability of oxytocin to induce erection is abolished by nitric oxide (NO) synthase inhibitors suggesting that oxytocin activates NO-synthase activity in the hippocampus (35). NO in turn activates glutaminergic neurotransmission (35). Inhibition of oxytocin with oxytocin antagonists reduced the number of mounts and intromissions in male rats, implicating a role for oxytocin in inducing male sexual behaviour (36).

In female rats, oxytocin can induce behaviours indicative of sexual receptivity such as increased quotient and duration of lordosis when infused into the ventromedial hypothalamus (VMH) and the medial preoptic area (MPO) (37). Administration to either area is dependent on steroid priming. Progesterone pretreatment is necessary for the induction of sexual behaviours in the VMH, whereas oestrogen priming is necessary for behaviour induction within the MPO (37).

In humans, higher levels of oxytocin are associated with increased arousal and sexual response as well as heightened catecholamine release during arousal (38). Oxytocin levels increase during intercourse and self-stimulation, and peak at orgasm in both sexes (39, 40) and is hypothesised to be important in inducing orgasm and sexual satiety (40).

Table 1 Summary of clinical trials being undertaken using oxytocin as an adjuvant or primary therapy as listed at www.clinicaltrials.gov.

Disease/disorder	Clinical trials identifier	Aim of clinical trial	Phase
Autism	NCT00490802	The effect of intranasal oxytocin in the treatment of autism	II
	NCT01183221	The effects of oxytocin on complex social cognition in adults with autism spectrum disorders	NS
	NCT00263796	To study the effect of oxytocin on face processing and response inhibition in autistic adults by functional magnetic resonance imaging	NS
	NCT01093768	To assess the effects of oxytocin and vasopressin on brain activity in healthy adult volunteers and adults with ASD using functional magnetic resonance imaging	NS
Schizophrenia	NCT00506909	To determine if intranasal oxytocin can augment the effects of antipsychotic medication in subjects who still suffer symptoms	NS
	NCT01028677	To test whether intranasal oxytocin improves social cognition, social functioning and decreases paranoia and other psychotic symptoms in schizophrenic subjects	NS
	NCT01123317	To determine if intranasal oxytocin changes regional brain blood flow to better understand the role of oxytocin in the modulation of social judgement	NS
	NCT00663039	To determine the efficacy of oxytocin nasal spray on social affiliation in schizophrenic patients	NS
	NCT00884897	To determine if oxytocin enhances emotional intelligence and improves performance on measures of social cognition in schizophrenic subjects	II
	NCT00813436	To identify the effect of intranasal oxytocin on empathic abilities in people with schizophrenia	II
	NCT00789022	To determine oxytocin levels in the plasma of patients before and after neuroleptic treatment following their first psychotic episode	NS
Anxiety	NCT00989937	To determine the efficacy of intranasal oxytocin to improve anxiety symptoms in a variety of anxiety disorders	NS
	NCT00975416	To determine whether intranasal oxytocin as an adjuvant to cognitive behavioural therapy for drug dependence alters treatment outcome	IV
	NCT01081249	To determine the effects of oxytocin on nonverbal behaviour in a psychotherapy session	NS
Pain	NCT00963040	To investigate the efficacy of intranasal oxytocin to reduce headache symptoms (nausea, vomiting, photophobia, phonophobia) in chronic headache	NS
	NCT00919802	To investigate the efficacy of intranasal oxytocin to reduce pain associated with interstitial cystitis	NS

NS, not specified.

Pair bonding

As with social affiliation, pair bonding has been most frequently studied in voles, particularly in prairie voles which display lifelong partner preference in response to mating and are monogamous (41). In female prairie voles, mating is associated with an increase in central oxytocin. This is thought to be a sufficient stimulus for the development as partner preference because it can be elicited in virgin females following oxytocin infusions into the left lateral ventricle. Furthermore, this effect is blocked by the administration of oxytocin receptor antagonists prior to mating (41). The development of partner preference is most probably as a result of an interaction between oxytocin receptors and dopamine receptors in the nucleus accumbens because blockade of either dopamine or oxytocin results in reduced partner preference (42).

Maternal behaviour

Oxytocin signalling in the brain is thought to be responsible for the development and strength of interactions between females and their offspring in mammals who display prolonged periods of maternal care. In female rats, intracerebroventricular injection of oxytocin can induce maternal behaviours such as licking, crouching and grouping of pups (43). These behaviours are partially dependent on the stage of the oestrous cycle that oxytocin administration occurs at, with the strongest induction of behaviours occurring in late dioestrous (43). In ewes, an increase in oxytocin levels following vaginocervical stimulation is associated with the onset of maternal behaviour (44). Increased central oxytocin levels are able to reduce aggression and foster the adoption of foreign lambs. These behaviours are dependent on oestrogen priming (44).

Virgin rats (45) and prairie voles (46) display a differential maternal response when exposed to pups. The range of responses varies from full adoption to rejection of pups. In both species, the oxytocin receptor content in the amygdala is higher in animals that foster young compared to those that exhibit aggressive behaviours (45, 46). In the polygamous montane vole, the onset of maternal behaviour is preceded by a redistribution of the oxytocin receptor in the brain (23). The importance of oxytocin in maternal behaviour has been highlighted by CD38 null mice. CD38 activation is thought to induce Ca^{2+}-mediated oxytocin release (44). Indeed, $CD38^{-/-}$ exhibit reduced amounts of plasma and cerebrospinal fluid (CSF) oxytocin and display blunted maternal behaviours that are rescued by oxytocin administration (47). These observations reflect those of oxytocin receptor knockout mice (26).

Stress

The anxiolytic effect of oxytocin has been examined most recently in oxytocin null mice (45). Anxiety behaviour, as measured using an open maze test, is increased in oxytocin null mice (48). Administration of oxytocin depresses this effect (48). The anxiolytic effects of oxytocin are mediated by altered cortisol and neurotransmitter release. Following acute stressors, such as isolation in a metabolic cage and rectal probing, female oxytocin null mice exhibit higher cortisol secretion compared with wild-type mice (49). Additionally, female oxytocin null mice exhibit increased mean arterial pressure compared with wild-type mice following chronic shaker stress (50). Altered pressor secretion is also noted but differs from that seen in acute stress, with a reduction in corticosterone release following chronic stress (50). Oxytocin has also been shown to exert anxiolytic effects by activation of oxytocin receptors of serotonergic neurons of the raphe nucleus and subsequent serotonin release (51).

In humans, intranasal oxytocin can induce a sense of calmness during a psychosocial stress test (52) and can reduce stress during couple conflict (33). In both studies, oxytocin administration was associated with a reduction in cortisol secretion (33, 52).

Cardiovascular functions

Oxytocin can reduce the blood pressure in isolated perfused hearts from cats, rabbits and chickens (53). The response of rabbit hearts is variable. Some show no response to oxytocin. Of those that do respond marked differences in the time course of action and magnitude are observed (53). The reduction is accounted for by decreased cardiac contractility and vasodilation. The ability of oxytocin to induce vasodilation (54) and reduce cardiac contractility (55) has been further illustrated in intact dogs. The fact that an effect is apparent in isolated hearts suggests that oxytocin can act locally. Indeed, oxytocin and its receptor are expressed within the heart (4, 56) and activation atrial oxytocin receptors are responsible for inducing atrial natriuretic peptide release that could explain the reduction in heart rate and contractility (56).

Oxytocin can also mediate blood pressure and heart rate responses centrally. Oxytocin neurons of the PVN are known to project into the vagal nerve and other cardiovascular centres in the brain (3). Oxytocin can increase vagal outflow to the heart accounting for the reduction in cardiac inotropy and chronotropy observed (57).

In spontaneously hypertensive rats, oxytocin levels are reduced in the PVN whereas dorsal brain stem oxytocin receptor expression is reduced following the onset of hypertension (58). The subsequent reduction in oxytocin responsiveness is hypothesised to mediate raised blood pressure. This is supported by the reduction in blood pressure following oxytocin treatment of spontaneously hypertensive rats (59). Moreover, chronic exercise results in an increase in PVN and dorsal brain stem oxytocin concentrations concomitant with a reduction in basal blood pressure (60). Similarly, exercise induces a rapid increase in oxytocin in the nucleus tractus solitarii. This effect blunts the tachycardic response to exercise as pretreatment with oxytocin antagonist prior to exercise potentiates the tachycardic response (61). Oxytocin null mice exhibit altered cardiovascular functions with a decrease in mean arterial pressure and reduced heart rate (50).

Functions in the male reproductive tract

Oxytocin and its receptor are expressed in the penis, testis, epididymis and sex accessory glands of many species (62). This is suggestive of a local oxytocinergic system operating in the male reproductive tract. Important roles for oxytocin in the testes have been proposed. First, it has been shown to affect steroidogenesis (63–65). Second, oxytocin can promote the arrival of sperm in the epididymis by inducing seminiferous tubule contraction in a dose-dependent (66) and spermatogenic stage-dependent (67) manner that promotes shedding of spermatozoa from the seminiferous epithelium (spermiation) (68). Spermiation is delayed in oxytocin null mice but is accelerated in mice overexpressing oxytocin (68). Similarly, the arrival of sperm in the epididymis can also be increased by oxytocin in the rat by increasing tubular transport and spermiation (69). Oxytocin also increases sperm movement through the epididymis by increasing spontaneous contractile activity (70). Circulating levels of oxytocin increase significantly during sexual arousal (39) and promote contractility of erectile tissues of the penis (71). Furthermore, oxytocin levels peak at orgasm (39, 72) and are thought to contribute to ejaculation by inducing intense contractions of pelvic muscles (72).

Targets for oxytocinergic signalling intervention

Oxytocin and its antagonist atosiban have been used clinically to manage labour for several years (73). Atosiban is the only antagonist approved for the pharmacological prevention of preterm delivery. It should be noted that this antagonist has a higher affinity to the vasopressin V1a receptor and displays greater antagonism than of the oxytocin receptor, suggesting an important role of V1a in human par-

turition. Oxytocin is available in several forms, including a nasal spray, and is generally well tolerated. Some side effects include nausea, headache, depression, anxiety and agitation (31, 74, 75). The availability of oxytocin and its antagonists and the vast array of functions of oxytocin make it an attractive option as an intervention for many pathologies. Several clinical trials have been conducted to date, with some ongoing. Most have concerned parturition management and social dysfunction. Other possible targets of oxytocinergic modulation have been identified and are reported here. However, the effects of long-term administration are poorly understood and require further determination. Despite only minor side effects being reported in recent clinical trials (74, 75), a male with obsessive compulsive disorder (OCD) that was treated with intranasal oxytocin for 4 weeks suffered memory disturbances, psychotic symptoms and a decrease in plasma sodium osmolality (76). Furthermore, some conditions can be contraindicated for the use of oxytocin therapy, such as benign prostatic hyperplasia and some cancers (reviewed below). Some clinical trials currently underway are outlined in Table 1, whereas outcomes of some trials and proposed pathologies for oxytocinergic-targeted therapies are summarised in Table 2.

Autism spectrum disorders

Autism spectrum disorders (ASDs) are marked by dysfunctional communication, repetitive motions and limited interests. Autistic subjects also display reduced eye gaze that results in an inability to identify subtle social cues such as emotions. Defects in the oxytocin signalling system, including reduced plasma oxytocin levels (77), have been identified

Table 2 Established and potential disease targets of oxytocin and oxytocin antagonist treatment.

Disease	Situation studied in	Effect of oxytocin	Method of intervention	References
Autism	Humans	• Decreased repetitive behaviours • Increased ability to identify emotions from speech and expression around eyes	Oxytocin	(74, 75, 81)
Schizophrenia	Humans	• Reduced scores on the positive and negative symptom scale	Oxytocin	(85)
	Animal models	• Reduced susceptibility to phencyclidine induced psychosis		(84)
Depression	Animals	• Decreased learned helplessness and behavioural despair	Oxytocin	(86, 87)
Anxiety disorders	Animals	• Reduced anxiety behaviour	Oxytocin	(51)
	Humans	• Reduced OCD symptoms • Improved outcome following exposure therapy with social phobia sufferers		(76, 93)
Cancer				
Breast cancer	Cell lines MDA-MB231	• Inhibition of cell proliferation	Oxytocin	(95)
Ovarian cancer	Cell lines SKOV3	• Inhibition of cell proliferation, migration and invasion	Oxytocin	(98)
	Athymic nude mice	• Decreased disseminated disease	Oxytocin	(98)
Small cell lung carcinoma	Cell lines DMS79, H146, and H345	• Inhibition of cell proliferation	Oxytocin antagonist	(94)
Prostate cancer	Cell lines			
	DU145	• Inhibition of cell proliferation	Oxytocin	(96)
	PC3	• Stimulation of cell proliferation	or Oxytocin	(96, 105)
	LNCaP	• Increased migration and invasion • No apparent effect	antagonist	
Endometrial cancer	Cell lines COLO 684	• Inhibition of cell proliferation	Oxytocin	(99)
BPH	Humans, dogs	• Increased prostatic tone • Increased prostatic growth	Oxytocin antagonist	(113, 114)
Pain	Humans, animals	• Analgesic effect • Increased pain threshold	Oxytocin	(115–117)
Injuries and inflammation	Animal models	• Reduced tissue destruction • Reduced inflammation	Oxytocin	(119–123)
Osteoporosis	Animal models	• Bone loss inhibited	Oxytocin	(129)

in subjects with ASDs and are thought to contribute to social aspects of the disease. Reduced plasma oxytocin levels can result from single nucleotide polymorphisms of the CD38 gene (78). Additionally, novel genetic polymorphisms in the oxytocin receptor gene, hypothesised to result in reduced affinity of oxytocin binding, have been identified in subjects with ASDs (79), as have decreased oxytocin receptor expression as a result of epigenetic silencing (80). The use of oxytocin to treat ASDs in clinical trials has produced promising results. Following intravenous injection of oxytocin, subjects show a significant reduction in the frequency and number of different repetitive behaviours. This effect was increased with time (75). Intranasal administration of oxytocin in ASD subjects results in improved performance in the 'seeing the mind in the eyes test' (81) where subjects are asked to assign emotions based on a photograph of a person's eyes (81). Additionally, intravenous oxytocin infusions have been associated with an increased capacity to infer the moods of others from their speech (affective speech comprehension) (74). These are the first reports of any pharmacological intervention that can acutely improve the social symptoms of autism.

Schizophrenia

Schizophrenia is marked with social detachment, memory defects and psychosis. Blood oxytocin is reduced in subjects with the disease, which can account for the social symptoms observed (82). Treatment with neuroleptics and antipsychotics is known to increase the activity of neurons in the PVN and SON and could, therefore, be responsible for increasing oxytocin levels and alleviating some of the observed symptoms (83). Despite this, patients often suffer from social and memory deficits and this has implicated oxytocin as an adjuvant treatment to antipsychotics. In addition to improving social functions, oxytocin can be important in reducing psychotic symptoms. Oxytocin null mice display increased susceptibility to psychosis induced by phencyclidine owing to altered glutamatergic functioning (84). A clinical trial using oxytocin as an adjunct therapy to antipsychotics in schizophrenia patients has indicated that oxytocin can be beneficial in treating aspects of the disease (85). Other trials are currently underway (Table 1).

Mood and anxiety disorders

Depression is a common disorder marked by a reduction in social functioning, sexual dysfunction, disinterest in activities, disturbances to sleep patterns, eating patterns and cognitive dysfunction. In addition to psychosocial symptoms, people with depression often experience physical symptoms such as fatigue and generalised body aches. Antidepressants act to increase serotonin secretion and activity. Side effects of antidepressants include fatigue, increased appetite, weight gain, sweating and dry mouth. Some of these symptoms could potentially be due to inhibition of oxytocin release. Therefore, oxytocin could be used as an adjuvant to alleviate these side effects. Indeed, oxytocin could be a potential candidate to replace the use of antidepressants. In animal models of depression, administration of oxytocin (86) and oxytocin agonists (87) can induce an antidepressive effect as indicated by a reduction in learned helplessness and behavioural despair. The ability of oxytocin to induce antidepressive effects potentially arises from the fact that oxytocin can be activated by antidepressant therapy and can potentiate some of its effects (88). In humans, however, the situation is somewhat more complicated. Oxytocin levels have been reported to be increased (89) or decreased (90) in depression, whereas chronic activation of the oxytocinergic system is indicated by an increase in the density of oxytocin neurons in the PVN (91). Moreover, depressed patients show dysregulated oxytocin responses in laboratory sessions with a significant increase in oxytocin secretion in an imagery session (92). Furthermore, in humans, oxytocin secretion appears to be unaffected by antidepressant therapy (89).

Oxytocin has also been identified as a potential agent to treat anxiety disorders such as social phobia and OCD. Indeed, oxytocin is known to have anxiolytic effects that are mediated by oxytocin induced release of serotonin in the raphe nucleus (50). In a case study in the 1980s a hospitalised subject suffering from worsening OCD and who was not responsive to behavioural or drug therapies had reduced OCD symptoms following treatment (76). Oxytocin administration in social phobia patients undergoing exposure therapy was able to improve outcomes (93).

Cancer

The oxytocin receptor is expressed in a large number of tumours and tumour cell lines including those derived from lung (94), breast (95), prostate (96), endometrium (97) and ovary (98). Oxytocin is known to be able to bind and activate functional receptors in these tumours altering cell proliferation and migration.

Proliferation Oxytocin treatment can increase proliferation of small cell lung carcinoma lines (94) and choriocarcinoma cells (99). By contrast, oxytocin inhibits cellular proliferation of breast (95), ovarian (98) and endometrial carcinoma cells (97). The reduction in proliferation in ovarian cancer cells has been illustrated *in vivo* following the injection of cells into the peritoneum of athymic nude mice (98). Prostate cancer cell lines show differential responses to oxytocin. DU145 prostate cancer cells are inhibited by oxytocin treatment, PC3 prostate cancer cells are stimulated by oxytocin treatment, whereas LNCaP cells are unaffected by oxytocin treatment (96).

The difference in proliferative effect of oxytocin appears to be due to ''G protein promiscuity''. That is, coupling of the oxytocin receptor to different G proteins is dependent on cell type and the localisation of the oxytocin receptor within the plasma membrane (100). In HEK293 when the oxytocin receptor was targeted to caveolin enriched domains, coupling to $G\alpha_q$ resulted in a transient ERK1/2 phosphorylation that stimulated cellular proliferation (101). Alternatively, when the oxytocin receptor is located outside of caveolar microdomains, it is coupled to $G\alpha_i$, ERK phosphorylation appears to be sustained with an antiproliferative effect observed (101) (Figure 3). The proliferative effects can thus be altered by

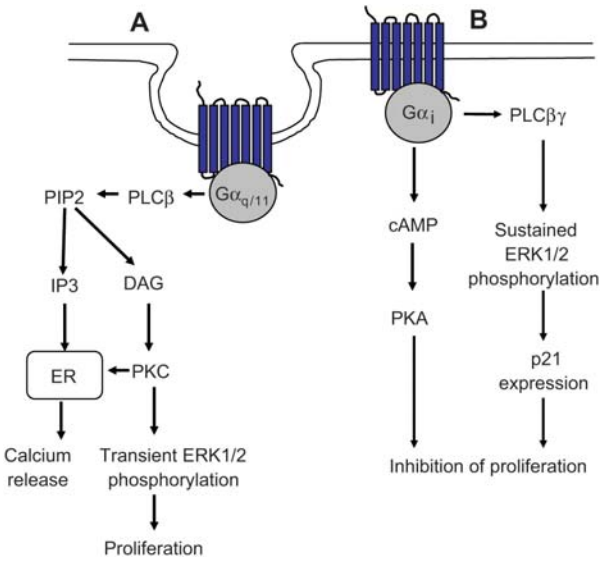

Figure 3 Proposed effects of oxytocin on target cell proliferation as determined by cellular localisation and G-protein-coupling. Pathway (A): oxytocin receptors located in caveolae preferentially couple to $G\alpha_{q/11}$ and activate a signalling cascade via phospholipase C-β (PLCβ), phosphatidylinositol-4,5-bisphosphate (PIP2), diacylglycerol (DAG) and protein kinase C (PKC). PKC activation induces the MAP-kinase pathway resulting in transient ERK1/2 phosphorylation and cell proliferation. Pathway (B): oxytocin receptors located outside of caveolae preferentially couple to $G\alpha_i$. Activation results in sustained ERK phosphorylation. This occurs through phospholipase C-βγ and subsequent cyclin dependent kinase inhibitor p21 expression, resulting in an inhibition of cell proliferation. A second pathway leads to an increase in cAMP, activation of protein kinase A and a consequent suppression of cell proliferation.

depleting the membrane of cholesterol or by targeting the oxytocin to caveolae (102, 103). Recent studies suggest that this situation is reversed in prostate cancer. Oxytocin-stimulated PC3 prostate cancer cells do not form caveolae because they lack the caveolae-essential protein, PTRF (104). By contrast, oxytocin-inhibited DU145 cells do form caveolae, and dispersal of caveolae with cyclodextrin reverses this antiproliferative effect (96). However, it is necessary to note that cyclodextrin removes cholesterol from the membrane and cholesterol is necessary for the proper functioning of G-protein-coupled receptors (1).

Migration In some tumour cell types, the effect of oxytocin on migration and invasion has been investigated. In PC3 cells, oxytocin stimulates migration. This is owing to a combined effect of EGFR transactivation and ERK1/2 phosphorylation initiated by signalling through $G\alpha_i$ (105). In ovarian SKOV3 cells, oxytocin treatment reduces migration and invasion *in vitro*. This is associated with a reduction in matrix metalloproteinase-2 activity and increased E-cadherin expression, reflecting reduced metastasis of these cells *in vivo* (98).

Angiogenesis In addition to affecting the proliferation of cancer cells directly, oxytocin can stimulate proliferation and migration of endothelial cells, and can induce capillary outgrowth (106, 107). In cancer and endometriosis this might have sinister implications. On a more positive aspect this implies that oxytocin might help in wound healing.

Dysregulation of oxytocin signalling in cancer cells

Normal oxytocinergic actions are thought to be altered in some cancers owing to dysregulated expression of both oxytocin and its receptor (Table 3). The most notable example of this is in small cell lung carcinomas which display increased oxytocin and oxytocin receptor expression, implicating oxytocin as an oncogenic factor through an autocrine/paracrine mechanism (94). By contrast, some prostate cancer cell lines and prostate tumours display decreased oxytocin expression but increased oxytocin receptor expression, most markedly following the acquisition of androgen independence (96). The implications of these alterations are unclear owing to the apparent heterogeneous effects of oxytocin on prostate cancer cell proliferation. In endometrial tumours, the oxytocin receptor redistributes to the cytoplasm in aggressive tumours. It is unclear how this arises but is proposed to

Table 3 Changes to oxytocin and oxytocin receptor expression in tumours and tumour cell lines.

Cancer	Cell line/tumour	Oxytocin	Oxytocin receptor	Implications	References
Prostate	PC3	Decreased expression	Increased expression	NI	(96, 105)
	DU145	Decreased expression (zero expression detected by PCR)	Increased expression	Reduced antitumorigenic actions of oxytocin	(96, 105)
	LNCap	Decreased expression	Increased expression	NI	(96)
	Adenocarcinomas	Decreased expression	Increased expression	NI	(96)
Endometrial	Tumours	NI	Translocates to cytoplasm when aggressive	Reduced antitumorigenic actions of oxytocin	(97)
Small cell lung carcinoma	Cell lines	Increased expression	Increased expression	Oxytocin acts as a mitogen via an autocrine/paracrine mechanism	(94)

NI, not identified.

reflect a loss of antitumorigenic action of oxytocin in these cell types (97).

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a disease in ageing males resulting primarily from overgrowth of the stroma in the periurethral and transition zones. It affects more than 50% of men over the age of 60 years (5, 108). The aetiology of BPH is unclear, but a significant factor is thought to be an increase in the oestrogen:androgen ratio that occurs with age (109). This stimulates prostatic secretion of oxytocin that is not subject to negative feedback regulation that is present in rodent prostates (110). The consequences of excessive oxytocin secretion can act to direct stromal cell growth indirectly by increasing the conversion of testosterone to dihydrotestosterone (DHT). Increased conversion of testosterone to DHT is enabled as oxytocin increases the activity of 5α reductase isoforms I and II and can additionally increase the expression of 5α II isoform in the rat ventral prostate (111). Similarly, oxytocin increases expression of 5α-reductase I and the activity of both isoforms of 5α-reductase in human prostatic epithelial cells (112). Moreover, oxytocin can contribute directly to the increased prostatic tone by increasing contraction of prostatic fibromuscular cells (113).

Nocioception

Oxytocin is thought to reduce the sensation of pain by intercepting pain signals at the level of the spinal cord and brain. Within the spinal cord, oxytocin triggers the release of glutamate from a distinct population of glutaminergic neurons. Glutamate excites GABAergic neurons resulting in synaptic inhibition in lamina II (114). Within the brain, the antinociceptive effect of oxytocin is probably as a result of an interaction between oxytocin and opioid receptor signalling (115). In rats, oxytocin administration can increase pain threshold as indicated by a reduced paw withdrawal time in response to mechanical and thermal stimulation (115). In humans, very low doses of oxytocin are effective in reducing the sensation of a finger prick (116).

Indeed, oxytocin signalling is dysregulated in pain conditions. In chronic back pain sufferers, oxytocin levels are reduced within the CSF and plasma, whereas in acute back pain sufferers, plasma oxytocin levels are reduced, but CSF levels are unchanged. The injection of oxytocin intrathecally eradicated or reduced pain in a large number of patients (117). Additionally, oxytocin is reduced in people with fibromyalgia, a chronic rheumatic condition marked by point tenderness in joints (118). The possibility of oxytocin use in pain management is the subject of current clinical trials investigating the effect of oxytocin on chronic headaches and interstitial cystitis, a chronic inflammatory condition of the bladder associated with pelvic pain (Table 1).

Injury and inflammation

In rats, ischemia and reperfusion injuries can be ameliorated by oxytocin pretreatment in the heart, liver and kidney but different mechanisms have been assigned to each. In the heart, oxytocin administration prior to ischemia could reduce infarct size owing to a reduction in coronary blood flow, and reduced metabolic demand of the tissue as indicated by a reduction in rate of contraction (119). In the liver, oxytocin administration prior to reperfusion prevented inflammation as indicated by reduced tumour necrosis factor (TNF) levels and neutrophil infiltration. Less tissue damage was also observed with a reduction in morphological damage, reduced plasma liver enzyme content and reduced free radical induced fibrosis (120). Similarly, oxytocin administration prior to reperfusion in the kidney could improve inflammation, tissue histopathology and renal function. In contrast to the liver, however, this was found to be as a result of reduced lipid peroxidation and reactive oxytocin species generation (121).

In rats, thermal skin injuries are associated with systemic effects including oxidative destruction of the gastric mucosa. Administration of oxytocin is effective at reducing both the localised and systemic injury associated with thermal injury (122). The reduction in cortisol observed within this study is suggestive of this being due to an anxiolytic effect of oxytocin, but anti-inflammatory and antipain effects are also implicated (122). Additionally, oxytocin can reduce atherosclerosis in $ApoE^{-/-}$ mice, again a result of oxytocins anti-inflammatory actions (123).

Anorgasmia and oligospermia

Oxytocin has been proposed for the treatment of anorgasmia and for improvement of sperm concentration of the ejaculate. In animals, oxytocin can increase semen volume and number of ejaculated sperm in rams (124), induce shedding of spermatozoa from the seminiferous tubules and induce sperm movement through the reproductive tract of rats, mice and rabbits (68, 69, 125). Furthermore, the peak of oxytocin at orgasm is highly suggestive that oxytocin contributes to ejaculation in humans (38, 72). In a case study of a male with anorgasmia, ejaculation was restored with intracoitally administered oxytocin (126). In the treatment of oligospermia, however, a single dose of oxytocin was ineffective in increasing sperm numbers in the ejaculate (127).

Osteoporosis

Both male and female mice lacking either oxytocin or the oxytocin receptor display severe loss of bone mass (osteoporosis) (128). Consistent with this, plasma oxytocin levels are significantly lower in osteoporotic postmenopausal women compared with non-osteoporotic women (129). Such bone loss can be inhibited by administration of oxytocin in a mouse model of osteoporosis (129). This action is modulated by the ability of oxytocin to induce osteoblast differentiation and mineralisation while inhibiting bone resorption by mature osteoclasts (128). By contrast, oxytocin increases the formation of osteoclasts (128, 130), and possibly transfer of calcium from mother to offspring during pregnancy (130). Hence, oxytocin might be important for maternal bone resorption and calcium mobilisation, and subsequent skeletal

remineralisation that is seen in pregnancy and lactation (130).

Expert opinion

Oxytocin has great potential for the treatment of disorders such as autism, schizophrenia and depression. To realise this potential, a greater understanding of the dysregulation within oxytocinergic systems is needed. To date, studies have only investigated alterations to CSF and circulating levels of oxytocin, and on polymorphisms in the oxytocin receptor. No studies have been performed on humans to determine changes in oxytocin receptor density or distribution in the brain that can account for altered sensitivity to oxytocin in people with these disorders. Studies performed thus far have indicated that not all people respond to oxytocin treatment. Furthermore, studies are required to determine systemic effects of long-term oxytocin treatment before this can be considered an option. Previous data has illustrated that long-term oxytocin can affect plasma osmolality and induce psychosis which, although reversible (76), are undesirable side effects with potentially devastating consequences. This review has identified several diseases that are potentially contraindicated for the use of oxytocin, such as some cancers and BPH, but that might benefit from oxytocin antagonist treatment. In terms of pain relief, there are some concerns that the actions of oxytocin are owing to a sedative effect rather than an actual reduction in pain (114, 117).

Outlook

We anticipate that research into oxytocinergic systems will continue to attract wide attention, particularly in areas of social behaviour and cognition. Within the past few years, the number of diseases being investigated with oxytocin treatment has increased and is bound to increase further. Once a greater understanding of the subtleties in oxytocin signalling that are evident between cell and tissue types is achieved it is expected that some of those pathologies in which oxytocin is implicated will be targeted for treatment by oxytocin or antagonists. Indeed, clinical trials of disorders such as schizophrenia and autism are already in stage II and stage IV with no adverse effects of oxytocin being reported. It is therefore probable that oxytocin will be implemented in the treatment of these disorders, where inadequate treatment is currently available.

Highlights

- Oxytocin is a highly pleiotropic hormone.
- Oxytocin mediates social behaviour and is thus seen as a potential treatment option for disorders associated with decreased social function such as autism, depression and schizophrenia.
- Oxytocin can alleviate physical injury by reducing inflammation, nocioception and associated stress, implicating oxytocin as a potential therapy of trauma.
- Oxytocin modulates cancer cell behaviour. Mechanisms are poorly understood and are being investigated.
- Oxytocin antagonists provide potential treatments for diseases where oxytocin could have sinister actions (e.g., some cancers and BPH).

Conflict of interest statement

N.C.T. is supported by an Australian Postgraduate Award and a Cancer Institute of New South Wales Research Scholar Award 10/RSA/1-31. S.J.A. is supported by a National Health and Medical Research Council Research Project grant 632778 and by the University of Sydney Cancer Research Fund.

References

1. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev 2001; 81: 629–83.
2. Du Vigneaud V, Ressler C, Trippett S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. J Biol Chem 1953; 205: 949–57.
3. Sofroniew MV. Projections from vasopressin, oxytocin, and neurophysin neurons to neural targets in the rat and human. J Histochem Cytochem 1980; 28: 475–8.
4. Jankowski M, Hajjar F, Kawas SA, Mukaddam-Daher S, Hoffman G, McCann SM, Gutkowska J. Rat heart: a site of oxytocin production and action. Proc Natl Acad Sci USA 1998; 95: 14558–63.
5. Nicholson HD, Whittington K. Oxytocin and the human prostate in health and disease. Int Rev Cytol 2007; 263: 253–86.
6. Harris GC, Frayne J, Nicholson HD. Epididymal oxytocin in the rat: its origin and regulation. Int J Androl 1996; 19: 278–86.
7. Gopal Rao VVN, Loffler C, Battey J, Hansmann I. The human gene for oxytocin-neurophysin I (OXT) is physically mapped to chromosome 20p13 by in situ hybridization. Cytogen Gen Res 1992; 61: 271–3.
8. Richard S, Zingg HH. The human oxytocin gene promoter is regulated by estrogens. J Biol Chem 1990; 265: 6098–103.
9. Richard S, Zingg HH. Identification of a retinoic acid response element in the human oxytocin promoter. J Biol Chem 1991; 266: 21428–33.
10. Adan RA, Cox JJ, van Kats JP, Burbach JP. Thyroid hormone regulates the oxytocin gene. J Biol Chem 1992; 267: 3771–7.
11. Dellovade TL, Zhu YS, Pfaff DW. Thyroid hormones and estrogen affect oxytocin gene expression in hypothalamic neurons. J Neuroendocrinol 1999; 11: 1–10.
12. Bossmar T, Osman N, Zilahi E, Haj MAE, Nowotny N, Conlon JM. Expression of the oxytocin gene, but not the vasopressin gene, in the rat uterus during pregnancy: influence of oestradiol and progesterone. J Endocrinol 2007; 193: 121–6.
13. Zingg HH, Laporte SA. The oxytocin receptor. Trends Endocrinol Metab 2003; 14: 222–7.
14. Nissenson R, Fluoret G, Hechter O. Opposing effects of estradiol and progesterone on oxytocin receptors in rabbit uterus. Proc Natl Acad Sci USA 1978; 75: 2044–8.
15. Tahara M, Morishige K-i, Sawada K, Ikebuchi Y, Kawagishi R, Tasaka K, Murata Y. RhoA/Rho-kinase cascade is involved

in oxytocin-induced rat uterine contraction. Endocrinology 2002; 143: 920–9.
16. Li Y, Je HD, Malek S, Morgan KG. ERK1/2-mediated phosphorylation of myometrial caldesmon during pregnancy and labor. Am J Physiol Reg Int Comp Physiol 2003; 284: R192–9.
17. Strakova Z, Copland JA, Lolait SJ, Soloff MS. ERK2 mediates oxytocin-stimulated PGE2 synthesis. Am J Physiol 1998; 274: E634–41.
18. Higuchi T, Tadokoro Y, Honda K, Negoro H. Detailed analysis of blood oxytocin levels during suckling and parturition in the rat. J Endocrinol 1986; 110: 251–6.
19. Antonijevic IA, Russell JA, Bicknell RJ, Leng G, Douglas AJ. Effect of progesterone on the activation of neurones of the supraoptic nucleus during parturition. J Reprod Fertil 2000; 120: 367–76.
20. Russell JA, Leng G, Douglas AJ. The magnocellular oxytocin system, the fount of maternity: adaptations in pregnancy. Front Neuroendocrinol 2003; 24: 27–61.
21. Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, Matzuk MM. Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. Proc Natl Acad Sci USA 1996; 93: 11699–704.
22. Douglas AJ, Leng G, Russell JA. The importance of oxytocin mechanisms in the control of mouse parturition. Reproduction 2002; 123: 543–52.
23. Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc Natl Acad Sci USA 1992; 89: 5981–5.
24. Campbell P, Ophir AG, Phelps SM, Campbell P, Ophir AG, Phelps SM. Central vasopressin and oxytocin receptor distributions in two species of singing mice. J Comp Neurol 2009; 516: 321–33.
25. Witt DM, Winslow JT, Insel TR. Enhanced social interactions in rats following chronic, centrally infused oxytocin. Pharmacol Biochem Behav 1992; 43: 855–61.
26. Takayanagi Y, Yoshida M, Bielsky IF, Ross HE, Kawamata M, Onaka T, Yanagisawa T, Kimura T, Matzuk MM, Young LJ, Nishimori K. Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. Proc Natl Acad Sci USA 2005; 102: 16096–101.
27. Scattoni ML, Gandhy SU, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in the BTBR T+tf/J mouse model of autism. PLoS ONE 2008; 3: e3067.
28. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature 2005; 435: 673–6.
29. Theodoridou A, Rowe AC, Penton-Voak IS, Rogers PJ. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav 2009; 56: 128–32.
30. Guastella AJ, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. Biol Psychiatry 2008; 63: 3–5.
31. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves ''mind-reading'' in humans. Biol Psychiatry 2007; 61: 731–3.
32. Rimmele U, Hediger K, Heinrichs M, Klaver P. Oxytocin makes a face in memory familiar. J Neurosci 2009; 29: 38–42.
33. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol Psychiatry 2009; 65: 728–31.
34. Chen K, Chang LS. Oxytocinergic neurotransmission at the hippocampus in the central neural regulation of penile erection in the rat. Urology 2001; 58: 107–12.
35. Melis MR, Succu S, Cocco C, Caboni E, Sanna F, Boi A, Ferri GL, Argiolas A. Oxytocin induces penile erection when injected into the ventral subiculum: role of nitric oxide and glutamic acid. Neuropharmacology 2010; 58: 1153–60.
36. Argiolas A, Collu M, Gessa GL, Melis MR, Serra G. The oxytocin antagonist d(CH2)5Tyr(Me)-Orn8-vasotocin inhibits male copulatory behaviour in rats. Eur J Pharmacol 1988; 149: 389–92.
37. Schulze HG, Gorzalka BB. Oxytocin effects on lordosis frequency and lordosis duration following infusion into the medial pre-optic area and ventromedial hypothalamus of female rats. Neuropeptides 1991; 18: 99–106.
38. Burri A, Heinrichs M, Schedlowski M, Kruger THC. The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. Psychoneuroendocrinology 2008; 33: 591–600.
39. Murphy MR, Seckl JR, Burton S, Checkley SA, Lightman SL. Changes in oxytocin and vasopressin secretion during sexual activity in men. J Clin Endocrinol Metab 1987; 65: 738–41.
40. Blaicher W, Gruber D, Bieglmayer C, Blaicher AM, Knogler W, Huber JC. The role of oxytocin in relation to female sexual arousal. Gynecol Obstet Invest 1999; 47: 125–6.
41. Insel TR, Hulihan TJ. A gender-specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. Behav Neurosci 1995; 109: 782–9.
42. Liu Y, Wang ZX. Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. Neuroscience 2003; 121: 537–44.
43. Pedersen CA, Prange AJ Jr. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. Proc Natl Acad Sci USA 1979; 76: 6661–5.
44. Keverne EB, Kendrick KM. Oxytocin facilitation of maternal behavior in sheep. Ann NY Acad Sci 1992; 652: 83–101.
45. Francis DD, Champagne FC, Meaney MJ. Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. J Neuroendocrinol 2000; 12: 1145–8.
46. Olazabal DE, Young LJ. Oxytocin receptors in the nucleus accumbens facilitate ''spontaneous'' maternal behavior in adult female prairie voles. Neuroscience 2006; 141: 559–68.
47. Jin D, Liu HX, Hirai H, Torashima T, Nagai T, Lopatina O, Shnayder NA, Yamada K, Noda M, Seike T, Fujita K, Takasawa S, Yokoyama S, Koizumi K, Shiraishi Y, Tanaka S, Hashii M, Yoshihara T, Higashida K, Islam MS, Yamada N, Hayashi K, Noguchi N, Kato I, Okamoto H, Matsushima A, Salmina A, Munesue T, Shimizu N, Mochida S, Asano M, Higashida H. CD38 is critical for social behaviour by regulating oxytocin secretion. Nature 2007; 446: 41–5.
48. Mantella RC, Vollmer RR, Li X, Amico JA. Female oxytocin-deficient mice display enhanced anxiety-related behavior. Endocrinology 2003; 144: 2291–6.
49. Amico JA, Cai H, Vollmer RR. Corticosterone release in oxytocin gene deletion mice following exposure to psychogenic versus non-psychogenic stress. Neurosci Lett 2008; 442: 262–6.
50. Bernatova I, Rigatto KV, Key MP, Morris M. Stress-induced pressor and corticosterone responses in oxytocin-deficient mice. Exp Physiol 2004; 89: 549–57.
51. Yoshida M, Takayanagi Y, Inoue K, Kimura T, Young LJ, Onaka T, Nishimori K. Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. J Neurosci 2009; 29: 2259–71.
52. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective

responses to psychosocial stress. Biol Psychiatry 2003; 54: 1389–98.
53. Woodbury RA, Abreu BE. Influence of oxytocin (pitocin) upon the heart and blood pressure of the chicken, rabbit, cat, dog and turtle. Am J Physiol 1944; 142: 114–20.
54. Lloyd S, Pickford M. The effect of oestrogens and sympathetic denervation on the response to oxytocin of the blood vessels in the hind limb of the dog. J Physiol 1962; 163: 362–71.
55. Mukaddam-Daher S, Yin YL, Roy J, Gutkowska J, Cardinal R. Negative inotropic and chronotropic effects of oxytocin. Hypertension 2001; 38: 292–6.
56. Gutkowska J, Jankowski M, Lambert C, Mukaddam-Daher S, Zingg HH, McCann SM. Oxytocin releases atrial natriuretic peptide by combining with oxytocin receptors in the heart. Proc Natl Acad Sci USA 1997; 94: 11704–9.
57. Higa KT, Mori E, Viana FF, Morris M, Michelini LC. Baroreflex control of heart rate by oxytocin in the solitary-vagal complex. Am J Physiol Reg Int Comp Physiol 2002; 282: R537–45.
58. Morris M, Keller M, Sundberg DK. Changes in paraventricular vasopressin and oxytocin during the development of spontaneous hypertension. Hypertension 1983; 5: 476–81.
59. Petersson M, Lundeberg T, Uvnas-Moberg K. Oxytocin decreases blood pressure in male but not in female spontaneously hypertensive rats. J Autonom Nervous Syst 1997; 66: 15–8.
60. Martins AS, Crescenzi A, Stern JE, Bordin S, Michelini LC. Hypertension and exercise training differentially affect oxytocin and oxytocin receptor expression in the brain. Hypertension 2005; 46: 1004–9.
61. Braga DC, Mori E, Higa KT, Morris M, Michelini LC. Central oxytocin modulates exercise-induced tachycardia. Am J Physiol Reg Int Comp Physiol 2000; 278: R1474–82.
62. Thackare H, Nicholson HD, Whittington K. Oxytocin – its role in male reproduction and new potential therapeutic uses. Hum Reprod Update 2006; 12: 437–48.
63. Adashi EY, Tucker EM, Hsueh AJ. Direct regulation of rat testicular steroidogenesis by neurohypophysial hormones. Divergent effects on androgen and progestin biosynthesis. J Biol Chem 1984; 259: 5440–6.
64. Frayne J, Nicholson HD. Effect of oxytocin on testosterone production by isolated rat Leydig cells is mediated via a specific oxytocin receptor. Biol Reprod 1995; 52: 1268–73.
65. Nicholson HD, Guldenaar SE, Boer GJ, Pickering BT. Testicular oxytocin: effects of intratesticular oxytocin in the rat. J Endocrinol 1991; 130: 231–8.
66. Worley RTS, Nicholson HD, Pickering BT. Testicular oxytocin: an initiator of seminiferous tubule movement. In: Saez JM, Forest MG, Dazard A, Bertrand J, editors. Recent Progress in Cellular Endocrinology of the Testis Paris: Colleques de l'INSERM 1985; 123: 205–12.
67. Harris GC, Nicholson HD. Stage-related differences in rat seminiferous tubule contractility in vitro and their response to oxytocin. J Endocrinol 1998; 157: 251–7.
68. Assinder SJ, Rezvani A, Nicholson HD. Oxytocin promotes spermiation and sperm transfer in the mouse. Int J Androl 2002; 25: 19–27.
69. Frayne J, Townsend D, Nicholson HD. Effects of oxytocin on sperm transport in the pubertal rat. J Reprod Fertil 1996; 107: 299–306.
70. Filippi S, Morelli A, Vignozzi L, Vannelli GB, Marini M, Ferruzzi P, Mancina R, Crescioli C, Mondaini N, Forti G, Ledda F, Maggi M. Oxytocin mediates the estrogen-dependent contractile activity of endothelin-1 in human and rabbit epididymis. Endocrinology 2005; 146: 3506–17.
71. Zhang XH, Filippi S, Vignozzi L, Morelli A, Mancina R, Luconi M, Donati S, Marini M, Vannelli GB, Forti G, Maggi M. Identification, localization and functional in vitro and in vivo activity of oxytocin receptor in the rat penis. J Endocrinol 2005; 184: 567–76.
72. Carmichael MS, Warburton VL, Dixen J, Davidson JM. Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. Arch Sex Behav 1994; 23: 59–79.
73. Clark SL, Simpson KR, Know E, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol 2009; 200: e1–e35.6.
74. Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L, Anagnostou E, Wasserman S. Oxytocin increases retention of social cognition in autism. Biol Psychiatry 2007; 61: 498–503.
75. Hollander E, Novotny S, Hanratty M, Yaffe R, DeCaria CM, Aronowitz BR, Mosovich S. Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. Neuropsychopharmacology 2003; 28: 193–8.
76. Ansseau M, Legros JJ, Mormont C, Cerfontaine JL, Papart P, Geenen V, Adam F, Franck G. Intranasal oxytocin in obsessive-compulsive disorder. Psychoneuroendocrinology 1987; 12: 231–6.
77. Green L, Fein D, Modahl C, Feinstein C, Waterhouse L, Morris M. Oxytocin and autistic disorder: alterations in peptide forms. Biol Psychiatry 2001; 50: 609–13.
78. Munesue T, Yokoyama S, Nakamura K, Anitha A, Yamada K, Hayashi K, Asaka T, Liu HX, Jin D, Koizumi K, Islam MS, Huang JJ, Ma WJ, Kim UH, Kim SJ, Park K, Kim D, Kikuchi M, Ono Y, Nakatani H, Suda S, Miyachi T, Hirai H, Salmina A, Pichugina YA, Soumarokov AA, Takei N, Mori N, Tsujii M, Sugiyama T, Yagi K, Yamagishi M, Sasaki T, Yamasue H, Kato N, Hashimoto R, Taniike M, Hayashi Y, Hamada J, Suzuki S, Ooi A, Noda M, Kamiyama Y, Kido MA, Lopatina O, Hashii M, Amina S, Malavasi F, Huang EJ, Zhang J, Shimizu N, Yoshikawa T, Matsushima A, Minabe Y, Higashida H. Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. Neurosci Res 2010; 67: 181–91.
79. Yrigollen CM, Han SS, Kochetkova A, Babitz T, Chang JT, Volkmar FR, Leckman JF, Grigorenko EL. Genes controlling affiliative behavior as candidate genes for autism. Biol Psychiatry 2008; 63: 911–6.
80. Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, Lintas C, Abramson RK, Wright HH, Ellis P, Langford CF, Worley G, Delong GR, Murphy SK, Cuccaro ML, Persico A, Pericak-Vance MA, Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, Lintas C, Abramson RK, Wright HH, Ellis P, Langford CF, Worley G, Delong GR, Murphy SK, Cuccaro ML, Persico A, Pericak-Vance MA. Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med 2009; 7: 62.
81. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hickie IB. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry 2010; 67: 692–4.
82. Goldman M, Marlow-O'Connor M, Torres I, Carter CS, Goldman M. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr Res 2008; 98: 247–55.
83. Kiss A, Bundzikova J, Pirnik Z, Mikkelsen JD. Different antipsychotics elicit different effects on magnocellular oxytocinergic and vasopressinergic neurons as revealed by Fos immunohistochemistry. J Neurosci Res 2010; 88: 677–85.

84. Caldwell HK, Stephens SL, Young WS 3rd. Oxytocin as a natural antipsychotic: a study using oxytocin knockout mice. Mol Psychiatry 2009; 14: 190–6.
85. Feifel D, Macdonald K, Nguyen A, Cobb P, Warlan H, Galangue B, Minassian A, Becker O, Cooper J, Perry W, Lefebvre M, Gonzales J, Hadley A. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol Psychiatry 2010; 68: 678–80.
86. Arletti R, Bertolini A. Oxytocin acts as an anti-depressant in two animal models of depression. Life Sci 1987; 41: 1725–30.
87. Chaviaras S, Mak P, Ralph D, Krishnan L, Broadbear JH. Assessing the antidepressant-like effects of carbtocin, an oxytocin agonist, using a modification of the forced swim test. Psychopharmacology 2010; 210: 35–43.
88. Uvnas-Moberg K, Bjorkstrand E, Hillegaart V, Ahlenius S. Oxytocin as a possible mediator of SSRI-induced antidepressant effects. Psychopharmacology 1999; 142: 95–101.
89. Ozsoy S, Esel E, Kula M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. Psychiatry Res 2009; 169: 249–52.
90. Frasch A, Zetzsche T, Steiger A, Jirikowski GF. Reduction of plasma oxytocin levels in patients suffering from major depression. Adv Exp Med Biol 1995; 395: 257–8.
91. Purba JS, Hoogendijk WJG, Hofman MA, Swaab DF. Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. Arch Gen Psychiatry 1996; 53: 137–43.
92. Cyranowski JM, Hofkens TL, Frank E, Seltman H, Cai H-M, Amico JA. Evidence of dysregulated peripheral oxytocin release among depressed women. Psychosom Med 2008; 70: 967–75.
93. Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 2009; 34: 917–23.
94. Pequeux C, Breton C, Hendrick J-C, Hagelstein M-T, Martens H, Winkler R, Geenen V, Legros J-J. Oxytocin synthesis and oxytocin receptor expression by cell lines of human small cell carcinoma of the lung stimulate tumor growth through autocrine/paracrine signaling. Cancer Res 2002; 62: 4623–9.
95. Cassoni P, Sapino A, Fortunati N, Munaron L, Chini B, Bussolati G. Oxytocin inhibits the proliferation of MDA-MB231 human breast-cancer cells via cyclic adenosine monophosphate and protein kinase A. Int J Cancer 1997; 72: 340–4.
96. Assinder SJ. Oxytocin in the pathophysiology of prostate cancer. In: Handbook of oxytocin research: synthesis, storage and release, actions and drug forms. New York: Nova Science, 2009.
97. Cassoni P, Fulcheri E, Carcangiu ML, Stella A, Deaglio S, Bussolati G. Oxytocin receptors in human adenocarcinomas of the endometrium: presence and biological significance. J Pathol 2000; 190: 470–7.
98. Morita T, Shibata K, Kikkawa F, Kajiyama H, Ino K, Mizutani S. Oxytocin inhibits the progression of human ovarian carcinoma cells *in vitro* and *in vivo*. Int J Cancer 2004; 109: 525–32.
99. Cassoni P, Sapino A, Munaron L, Deaglio S, Chini B, Graziani A, Ahmed A, Bussolati G. Activation of functional oxytocin receptors stimulates cell proliferation in human trophoblast and choriocarcinoma cell lines. Endocrinology 2001; 142: 1130–6.
100. Reversi A, Rimoldi V, Marrocco T, Cassoni P, Bussolati G, Parenti M, Chini B. The oxytocin receptor antagonist atosiban inhibits cell growth via a ''biased agonist'' mechanism. J Biol Chem 2005; 280: 16311–8.
101. Rimoldi V, Reversi A, Taverna E, Rosa P, Francolini M, Cassoni P, Parenti M, Chini B. Oxytocin receptor elicits different EGFR/MAPK activation patterns depending on its localization in caveolin-1 enriched domains. Oncogene 2003; 22: 6054–60.
102. Guzzi F, Zanchetta D, Cassoni P, Guzzi V, Francolini M, Parenti M, Chini B. Localization of the human oxytocin receptor in caveolin-1 enriched domains turns the receptor-mediated inhibition of cell growth into a proliferative response. Oncogene 2002; 21: 1658–67.
103. Reversi A, Rimoldi V, Brambillasca S, Chini B. Effects of cholesterol manipulation on the signaling of the human oxytocin receptor. Am J Physiol Reg Int Comp Physiol 2006; 291: R861–9.
104. Hill M, Bastiani M, Luetterforst R. PTRF-Cavin, a conserved cytoplasmic protein required for caveolae formation and function. Cell 2008; 132: 113–24.
105. Zhong M, Boseman ML, Millena AC, Khan SA. Oxytocin induces the migration of prostate cancer cells: involvement of the G_i-coupled signaling pathway. Mol Cancer Res 2010; 8: 1164–72.
106. Cattaneo MG, Chini B, Vicentini LM. Oxytocin stimulates migration and invasion in human endothelial cells. Br J Pharmacol 2008; 153: 728–36.
107. Thibonnier M, Conarty DM, Preston JA, Plesnicher CL, Dweik RA, Erzurum SC. Human vascular endothelial cells express oxytocin receptors. Endocrinology 1999; 140: 1301–9.
108. Assinder SJ, Nicholson HD. Prostate disease: prostate hyperplasia, prostate cancer and prostatitis. In: Kandeel FR, Swerdloff RS, Pryor JL, editors. Male reproductive dysfunction: pathophysiology and treatment. (Eds Jastrow H, Feuerbach D) New York: Informa Healthcare, 2007: pp. 155–70.
109. King KJ, Nicholson HD, Assinder SJ. Effect of increasing ratio of estrogen: androgen on proliferation of normal human prostate stromal and epithelial cells, and the malignant cell line LNCaP. Prostate 2006; 66: 105–14.
110. Assinder SJ, Nicholson HD. Effects of steroids on oxytocin secretion by the human prostate *in vitro*. Int J Androl 2004; 27: 12–8.
111. Assinder SJ, Johnson C, King K, Nicholson HD. Regulation of 5α-reductase isoforms by oxytocin in the rat ventral prostate. Endocrinology 2004; 145: 5767–73.
112. Assinder SJ. Oxytocin increases 5α-reductase activity of human prostate epithelial cells, but not stromal cells. Prostate 2008; 68: 115–21.
113. Bodanszky M, Sharaf H, Roy JB, Said SI. Contractile activity of vasotocin, oxytocin, and vasopressin on mammalian prostate. Eur J Pharmacol 1992; 216: 311–3.
114. Breton JD, Veinante P, Uhl-Bronner S, Vergnano AM, Freund-Mercier MJ, Schlichter R, Poisbeau P. Oxytocin-induced antinociception in the spinal cord is mediated by a subpopulation of glutamatergic neurons in lamina I–II which amplify GABAergic inhibition. Mol Pain 2008; 4: 19.
115. Gao L, Yu L. Involvement of opioid receptors in the oxytocin-induced antinociception in the central nervous system of rats. Regul Peptid 2004; 120: 53–8.
116. Uryvaev YV, Petrov GA. Extremely low doses of oxytocin reduce pain sensitivity in men. Bull Exp Biol Med 1995; 11: 1071–3.
117. Yang J. Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. Spine 1994; 19: 867–71.

118. Anderberg UM, Uvnas-Moberg K. Plasma oxytocin levels in female fibromyalgia syndrome patients. Z Rheumatol 2000; 59: 373–9.
119. Ondrejcakova M, Ravingerova T, Bakos J, Pancza D, Jezova D. Oxytocin exerts protective effects on in vitro myocardial injury induced by ischemia and reperfusion. Can J Physiol Pharmacol 2009; 87: 137–42.
120. Dusuncekum F, Iseri SO, Ercan F, Gedik N, Yegen C, Yegen BC. Oxytocin alleviates hepatic ischemia-reperfusion injury in rats. Peptides 2008; 29: 1216–22.
121. Tugtepe H, Sener G, Biyikli NK, Yuksel M, Cetinel S, Gedik N, Yegen BC. The protective effect of oxytocin on renal ischemia/reperfusion injury in rats. Regul Peptid 2007; 140: 101–8.
122. Iseri SO, Gedik IE, Erzik C, Uslu B, Arbak S, Gedik N, Yegen BC. Oxytocin ameliorates skin damage and oxidant gastric injury in rats with thermal trauma. Burns 2008; 34: 361–9.
123. Nation DA, Szeto A, Mendez AJ, Brooks LG, Zaias J, Herderick EE, Gonzales J, Noller CM, Schneiderman N, McCabe PM. Oxytocin attenuates atherosclerosis and adipose tissue inflammation in socially isolated $ApoE^{-/-}$ mice. Psychosom Med 2010; 72: 376–82.
124. Knight TW. The effect of oxytocin and adrenaline on the semen output of rams. J Reprod Fertil 1974; 39: 329–36.
125. Gupta J, Russell R, Wayman C, Hurley D, Jackson V. Oxytocin-induced contractions within rat and rabbit ejaculatory tissues are mediated by vasopressin V1A receptors and not oxytocin receptors. Br J Pharmacol 2008; 155: 118–26.
126. Ishak WW, Berman DS, Peters A, Ishak WW, Berman DS, Peters A. Male anorgasmia treated with oxytocin. J Sex Med 2008; 5: 1022–4.
127. Byrne MM, Rolf C, Depenbusch M, Cooper TG, Nieschlag E. Lack of effect of a single i.v. dose of oxytocin on sperm output in severely oligozoospermic men. Hum Reprod 2003; 18: 2098–102.
128. Tamma R, Colaianni G, Zhu LL, DiBenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, Colucci S, Grano M, Faccio R, Liu X, Li J, Usmani S, Bachar M, Bab I, Nishimori K, Young LJ, Buettner C, Iqbal J, Sun L, Zaidi M, Zallone A. Oxytocin is an anabolic bone hormone. Proc Natl Acad Sci USA 2009; 106: 7149–54.
129. Elabd C, Basillais A, Beaupied H, Breuil V, Wagner N, Scheideler M, Zaragosi LE, Massiera F, Lemichez E, Trajanoski Z, Carle G, Euller-Ziegler L, Ailhaud G, Benhamou CL, Dani C, Amri EZ. Oxytocin controls differentiation of human mesenchymal stem cells and reverses osteoporosis. Stem Cells 2008; 26: 2399–407.
130. Liu X, Shimono K, Zhu LL, Li J, Peng Y, Imam A, Iqbal J, Moonga S, Colaianni G, Su C, Lu Z, Iwamoto M, Pacifici M, Zallone A, Sun L, Zaidi M, Oxytocin deficiency impairs maternal skeletal remodeling. Biochem Biophys Res Commun 2009; 388: 161–6.