Oxytocin in the human – regulation of derivations and destinations

John J Evans

University Department of Obstetrics and Gynaecology, Christchurch School of Medicine, Christchurch, New Zealand

Introduction

Those of us who study physiology are tempted to hope that the experimental perturbations which we induce affect only the organ which has ensnared our interest. This review uses physiological systems which incorporate oxytocin as models to indicate some of the ways in which departure from such investigative paradise occurs, and also to discuss some of the implications of a physiology which uses one compound in several distinct roles.

The dual activities of oxytocin, on the uterus and on the mammary gland, for some time constituted the complete portfolio of the peptide’s functions in biology (1). However, now no longer is consideration of oxytocin confined to its two traditional roles. Investigations of oxytocin have demonstrated that oxytocin participates in a wide variety of activities in dispersed regions of the body, and is an element of the physiology of both sexes. Oxytocin is involved with sex, pain and moods, and its sites of action include the thymus, the ovary, and the pancreas.

After the oxytocic activity and the milk ejecting activity of the posterior pituitary gland were recognised, a nonapeptide was found to be responsible for the effects. The structure of the compound was established (2, 3) and oxytocin was the first peptide hormone to be purified and synthesised, and available for pharmaco-logically defined studies. Modern molecular biology has provided information of the oxytocin system (Fig. 1). The oxytocin gene has been mapped to 20p13 (4) although the nature of the regulatory elements critical to cell-specific expression of the oxytocin gene are still ill-defined (5). The molecular structure of the oxytocin receptor has been characterised (6) and the gene has been localised to 3p25–3p26 (7–9). It is assumed that oxytocin has evolved by duplication of an ancestor gene which oxytocin and vasopressin have in common. The vasopressin/oxytocin prohormone ancestor was present in Archaemetazoa, from which vertebrates and invertebrates diverged 600 million years ago (10, 11).

This review is designed first to serve as a reminder that a compound can affect multiple entities, secondly to consider some of the processes which control interaction between physiological units, and thirdly to point to the multifaceted effects, including alterations of behaviour, a pathological change can have. A variety of control mechanisms which are incorporated into oxytocin systems are summarised in Table 1 and corresponding examples indicated in the text by upper case letters (A–O). This review considers effects induced by oxytocin which have been observed in human studies, which after all is the ultimate target of most projects, with only occasional reference to antecedent animal investigations. Although animal studies have suggested several activities for oxytocin which are not discussed in this review it is necessary to note that there are some functions of oxytocin which are species specific. Examples are the apparently opposite effects of oxytocin on adrenocorticotrophin (ACTH) in humans (in which oxytocin is reported to be inhibitory) and in rats (in which oxytocin is stimulatory); another is the differences in the temporal profile of oxytocin in the cerebrospinal fluid (CSF) of humans and rats; a third is the distribution of oxytocin binding sites in the brain.

The brain

The hypothalamus is the traditionally recognised primary site of oxytocin synthesis. Studies of the human hypothalamus have shown the presence of neurones which contain immunoreactive oxytocin and oxytocin mRNA. The organisation of the neurones is similar to that in other mammals (12). Also oxytocin has been detected in several extrahypothalamic areas of the brain (13, 14). Regulating agents for oxytocin (e.g. opioids, neurotransmitters, products of the gonads and thyroid) act via receptors on oxytocin-containing neurones. Only some neurones possess the receptors and thus there is a selectivity of oxytocin activation at the transcriptional level (Table 1, A) (15, 16). Further control might be exacted in post-transcriptional processing in the production of polyA tail size of oxytocin mRNA, which correlates to oxytocin mRNA accumulation (Table 1, B) (17). The effect is possibly a result of enhanced mRNA stability and increased half life and also modified translational efficiency.

In addition oxytocin has been measured in CSF of humans and exhibits a time-dependent rhythm.
although such does not occur in the blood. The oxytocin in CSF is probably derived from neurones which extend to the third ventricle, the limbic system, the brain stem and the spinal cord (18).

From the hypothalamus oxytocin is transported to the posterior pituitary gland, the main source of oxytocin detected in the periphery during lactation and parturition. The release of oxytocin from the neurohypophysis is partly modulated by the reproductive endocrine environment (19, 20), although the presence of an oxytocin-like peptide is a complicating factor (21). Other factors are also potential participants in oxytocin regulation. These include angiotensin-II which increases oxytocin release, an effect enhanced by opioid antagonist, indicating involvement of an opioid mechanism (22). Pro-opiomelanocortin-derived peptides have been detected in the neurohypophysis of the human, consistent with a role of these compounds in oxytocin neurosecretion (23).

Binding of oxytocin in the brain of the human is present in regions which suggest oxytocin-mediated modulation might be involved in sensory, autonomic and motor processing mechanisms and other basal ganglia-related functions (24). Sex differences in oxytocin receptor distribution, which has implications for gender-specific processes, are apparently linked to regulation mediated by gonadal steroids (25). A differential control of receptors apparently occurs in brain (Table 1, C). Some oxytocin receptors are transient and present only during infancy or during maturation, some are regulated by gonadal steroids and some are present constantly (24).

**Lactation and the breast**

One of the traditional activities of oxytocin is in lactation. There is substantial evidence that nursing is a potent stimulus for oxytocin release from the neurohypophysis (26, 27). The reflex which elicits
besides the uterus have also been observed. Mothers
feeding (27). Uterine contractions have been reported during breast
clinically inducing contraction at term. In addition
an oxytocin response, has been proposed as a means of
oxytocin (32). In fact breast stimulation, which elicits
followed or were concomitant with an increase in
caused contractions of the uterus at term which
ition. Stimulation of the breast by electrical impulses
two traditional targets of oxytocin provides an illustra-
physiologically distinct system. Consideration of the
response to a specific stimulus can interfere in a
entities, as mentioned above, raises the possibility that a
partum period (31).

breast is most responsive to oxytocin during the post
modulated by the endocrine environment and the
was increased (30). The sensitivity of the tissue is
plateau pattern, and at high doses of oxytocin cAMP
stimulatory hormone
potential control mechanisms in oxytocin-mediated systems.

Table 1 Potential control mechanisms in oxytocin-mediated systems.

(1) Production
A Modulation of receptors of regulating agents, e.g. receptors for oestradiol, opioids.
B mRNA polyA tail length to modify post-transcriptional control.
H Different type of stimulus, such as act at the PVN (neurotransmitter-mediated) or the ovary (hormonal).

(2) Target
Interaction at oxytocin receptor
C Changes in receptors due to developmental stage in the brain.
E Alteration in receptor number by other hormones, e.g. by steroids in the uterus during pregnancy.
G Receptor subtype, having tissue-specific function.
K Different forms of oxytocin inducing distinct effects.
L Cyclical alterations in tissue composition, e.g. in the ovary or pituitary of females.

Post receptor
D Pattern of delivery to affect response, e.g. pulsatile delivery to the breast during lactation.
P Interaction by regulating agents with the intracellular response to oxytocin, e.g. by steroids.
M Target cell-dependent coupling to G-proteins.
N Composite requirements for activation of target gene.
O Tissue-specific activation of target response.

(3) Compartmentalisation
I Paracrine autocrine system constraints.
J The blood–brain barrier.

The table is divided into three categories: (1) controls exerted at the site of oxytocin production; (2) controls at the target site; (3) controls which rely on separation of systems into biological compartments. The upper case letters reference the control mechanisms to some examples in the text.

Oxytocin release (28) is activated before the tactile
stimulus of suckling occurs, and oversees a pulsatile
pattern of secretion (29). Because the delivery pattern of stimulatory hormone can profoundly affect the response of the target cells (Table 1, D) then some of the regulation of the downstream processes which control the response to oxytocin can be under the modulation of oxytocin itself. One of the most well known examples is the priming effect of pulsatile gonadotrophin-releasing hormone and the desensitisising effect of continuous exposure of gonadotrophs to this peptide.

In vitro studies clearly demonstrated a responsivity of breast tissue to oxytocin. Oxytocin induced a dose–response increase in intracellular Ca2+ with a peak-plateau pattern, and at high doses of oxytocin cAMP was increased (30). The sensitivity of the tissue is modulated by the endocrine environment and the breast is most responsive to oxytocin during the post partum period (31).

The involvement of oxytocin in several physiological entities, as mentioned above, raises the possibility that a response to a specific stimulus can interfere in a physiologically distinct system. Consideration of the two traditional targets of oxytocin provides an illustration. Stimulation of the breast by electrical impulses caused contractions of the uterus at term which followed or were concomitant with an increase in oxytocin (32). In fact breast stimulation, which elicits an oxytocin response, has been proposed as a means of clinically inducing contraction at term. In addition uterine contractions have been reported during breast feeding (27).

An interaction between lactation and other systems besides the uterus have also been observed. Mothers know that during feeding a quiet place is optimum. A study reported a reduction in the oxytocin response associated with breast feeding when stresses of arithmetic or noise were provided (33). Conversely lactation suppresses the stress axis. Suckling is associated with a prompt decline in plasma cortisol, consistent with observations that oxytocin suppresses ACTH (34, 35) (see below). Nevertheless the lactation–stress connection apparently consists of more than oxytocin and ACTH. Lactating women were observed to have a blunted ACTH and cortisol and glucose responses to exercise stress but oxytocin levels did not differ and were therefore probably not a factor in this exercise-induced modification (36). However there might have been modulatory processes activated by oxytocin secreted from magnocellular nuclei into central, mediating pathways.

Other, biochemical-initiated stimuli also affect the oxytocin response; in non-pregnant women ethanol inhibited the oxytocin rise induced by breast stimulation. It seemed that the oxytocin-induced rise was by a pathway independent of opioids, whereas the ethanol inhibition partially involved opioid peptides (37). Ethanol, orally in one of its palatable forms or intravenously, has been utilised to delay or suppress uterine contractions, a process which involves oxytocin (see below).

The relationship of oxytocin to the breast led to the question of whether there is a connection between oxytocin activity and breast cancer. In fact oxytocin receptors and oxytocin receptor mRNA have been found in breast cancer tissue, suggesting a site of action. It has been observed that oxytocin inhibits growth of breast cancer cells (38), although other studies suggest that it is without effect (39), or that it stimulates cancer
growth (40). Hence the effect of oxytocin in this context remains uncertain. However oxytocin might have an indirect effect on breast cancer development. Oxytocin stimulates contraction of myoepithelial cells in non-pregnant women and so possibly aids elimination of carcinogens generated by superoxide free radicals. It has therefore been proposed that activities which promote oxytocin levels are protective (41).

The uterus

The pregnant uterus is one of the traditional targets of oxytocin and at around the onset of labour uterine sensitivity to oxytocin markedly increases. Oxytocin receptors are present in the pregnant myometrium; receptor protein increases during the course of pregnancy (42). Oxytocin receptor mRNA is heterogeneously expressed in the tissue, also increasing during pregnancy reaching a peak after the onset of labour. Thus modulation of oxytocin receptor is an effective control mechanism (Table 1, E). It must be remembered that parturition involves a complex series of processes, the interaction of oxytocin with its receptor being only one of them. For example there is a relatively large amount of oxytocin receptor mRNA expression at 32 weeks’ gestation, but the uterus is still refractory at this time.

The involvement of oxytocin in stimulating contractility in labour is by G-protein-mediated processes which activate phospholipase C and mobilise calcium. It seems that the presence of oestriadiol is an important factor in enhancing the response of the myometrium to oxytocin, facilitating phospholipase C activation at a post-receptor level (43, 44). In addition an interaction between progesterone and oxytocin in their effects on the contractile activity of human myometrium has been observed (45). The relationships illustrate the possibility of regulatory (in this case steroidal) processes interacting with an oxytocin-targeted system (Table 1, F). In the case of the response of the myometrium to oxytocin, there appears to be multiple sites for regulation and possible interaction with other receptors (43). Interestingly, in view of the interaction between oxytocin and the stress axis, it has been observed that there is a synergism between oxytocin and corticotrophin-releasing hormone (CRH) in the contractile response of the myometrium, a process which is probably dependent on prostaglandin F2α (PGF2α) (46). The participation of oxytocin receptors in uterine function has led to investigations of the use of oxytocin antagonists in premature labour (47) and also in amelioration of dysmenorrhoea (48).

Oxytocin receptors are also present in the non-pregnant human uterus but the concentrations are much less than during pregnancy (42, 49). There seemed to be a higher concentration of receptor mRNA in the glandular epithelial cells at the time of ovulation, suggesting a biological function of oxytocin during the menstrual cycle (50). It appears therefore that oxytocin participates in the network which constitutes the functioning of endometrial glandular cell function. Binding studies also found a higher concentration at midcycle (51) in contrast to another investigation which observed a rise in receptor density in the late luteal phase and during menstruation. The latter results suggested a role of oxytocin in increasing uterine activity during menstruation (52). The function of oxytocin on the non-pregnant uterus is therefore yet to be resolved. It is possible that part of the process of development of pregnancy involves interaction of oxytocin with the uterus and it has been observed that in subfertile patients the concentration of endometrial oxytocin binding sites is less than in normal women. Treatment with clomiphene increased the concentrations to normal (51).

At the target cell, the control of oxytocin receptors provides a means of modulating oxytocin-mediated effects. Organs (e.g. the uterus) having receptors for modulating agents (e.g. oestrogens) which are responsible for up-regulating oxytocin receptor numbers, are able to remain quiescent in spite of occasionally raised oxytocin levels. In addition other hormones regulate their own receptors (53, 54) and by analogy there might be cases where oxytocin can control its own receptor.

There is also potential for regulation of oxytocin activity using receptor type (Table 1, G). The existence of subtypes of oxytocin receptors has been postulated (55) but the situation, particularly in the human, is yet far from clear. Distinct subtypes which are differentially regulated provides for separate activities of the same hormone. Examples abound in endocrinology, one of which is the sister hormone of oxytocin, vasopressin. In a more recently emerged model, human pituitary adenylate cyclase activating polypeptide receptor exhibits splice variants which coupled to dual signal transduction cascades to elicit possibly tissue-specific responses (56). In addition, human endothelin receptor exhibits a splice variant with possibly distinct functions (57). Another means of regulation is illustrated by angiotensin-II which alters expression of its own receptor subtype in a tissue-specific manner (58).

The ovary

Oxytocin and oxytocin receptors have been detected in the ovary which provides a clear illustration of the increasingly recognised need to expand considerations of oxytocin activity into non-traditional areas.

Granulosa cells

Granulosa cells of the ovarian follicle synthesise oxytocin and secrete it when stimulated with human chorionic gonadotrophin (hCG) (59, 60). Conversely granulosa cells respond to oxytocin (Fig. 2). Oxytocin decreased follicle-stimulating hormone (FSH)-stimulated oestradiol
release from cells with suitable characteristics (61). Oxytocin increased intracellular Ca$^{2+}$ in granulosa-lutein cells in culture and increased hCG-stimulated progesterone release (62). Oxytocin, acting via G$\alpha_{q,11}$ and G$i$-mediated phospholipase C activation, increased inositol phosphate formation and intracellular Ca$^{2+}$ (63). The presence of both oxytocin secretion and oxytocin-induced responses reveal the capacity for an autocrine regulatory mechanism.

**Cumulus**

In the cumulus expression of both oxytocin genes and oxytocin receptor genes have been detected (64, 65). The results suggest that locally produced oxytocin induces effects through ligand–receptor interaction. It has been suggested that oxytocin thereby modulates the functions of cumulus cells in a paracrine or autocrine manner and perhaps participates in fertilisation and early embryonic development.

**Corpus Luteum**

Oxytocin has also been detected in the corpus luteum (CL) (66), and the CL synthesises oxytocin (60). In addition oxytocin receptors have been detected (66, 67). However the CL responds to oxytocin in a complex manner and the role(s) of oxytocin with regard to the human CL are yet to be defined. In young CL, oxytocin stimulated oestradiol production which stimulated progesterone release but in addition oxytocin had a direct inhibitory effect on progesterone secretion (68). Oxytocin appears to interact, locally, with PGF$2\alpha$ in the luteolytic control of the CL (69) perhaps in a manner analogous to that observed in other species. There is therefore apparently the potential for oxytocin to act on cells to increase or decrease metabolite function depending on cellular state.

The ovary provides a well documented example of an extrahypothalamic site of oxytocin production. Distinct types of control (neurohumoral versus hormonal) regulate oxytocin synthesis and release at the different sites (e.g. hypothalamo–neurohypophysial axis and say the ovary) (Table 1, H). Thus the stimuli associated with lactation predicate activation of only certain systems which act to increase oxytocin at the brain and release oxytocin from storage in the neurohypophysis and will not target release or synthesis from say granulosa cells. Similarly the control mechanisms acting on the peripheral organs selectively do not affect oxytocin in the neurohypophysis and so when there is stimulation of release from a peripheral site of production then there is no concomitant increase in circulating oxytocin from the neurohypophysis.

In the several oxytocin systems which are paracrine/autocrine there is no delivery of significant levels of oxytocin into the peripheral circulation and to the anatomically separated systems. Large amounts of oxytocin are necessary to have a secondary effect because of the efficiency of metabolism and the consequent short half life of oxytocin. Thus the response is anatomically constrained to a tissue, by the use of paracrine/autocrine physiological units which localise the stimulus and immediate effects (Table 1, I).

**The Testis**

Oxytocin has been detected in extracts of the human testis (70), and possibly has a role in testicular steroidogenesis, being observed in higher amounts in testes with maturation arrest (71). Evidence for mRNA transcription has been obtained in the human testis although at a relatively low level. The biological significance of oxytocin in the testes is therefore uncertain (72), although there is evidence for an autocrine/paracrine oxytocinergic system in the Leydig cell compartment (73). This together with data from studies in other model systems strongly suggest participation by oxytocin in male reproductive physiology (74).

**The Thymus**

The importance of the roles of oxytocin in reproductive function (both physiological and behavioural) implies that immune recognition of the oxytocin self-antigen is necessary. This appears to be achieved by imprinting molecular self-identity in the thymus. The thymus induces central T-cell tolerance by clonal deletion of self-reactive T cells. Oxytocin is present and synthesised locally in the thymus (75, 76). Involvement of oxytocin in communication between human thymic epithelial cells and immature T cells in the development of immune tolerance has been suggested (77). Indeed
some immune pathologies can be explained by thymic oxytocin being involved in T cell positive selection and activation. An immune disequilibrium such as that of post partum seems to be partly induced by hypersecretion of oxytocin which activates an immune response. Oxytocin seems to be more definitively defined as a self molecule than vasopressin, a conclusion which is reached partly by examination of some pathologies such as an autoimmune aggression against vasopressin-producing neurones which results in central diabetes insipidus (76).

In sexual activity

The range of activities of oxytocin is emphasised by its apparent role also in sexual activity.

Levels of circulating oxytocin change during sexual activity (78, 79) (Fig. 3). It is possible that at least some of oxytocin’s role in this context is related to its well known ability to stimulate contraction of smooth muscles, in this case the muscles in the genital–pelvic area. Also oxytocin action during sexual activity partly perhaps involves its effects on behaviours, and oxytocin might serve as a neuromodulator and affect cerebral neurones responsible for the cognitive feelings of orgasm and/or may sensitise cerebral neurones associated with pelvic floor striated muscle contractions (80). In addition oxytocin might be involved prior to coitus, in sexual arousal. Psychological changes during sexual arousal have been reported to correspond to changes in oxytocin (81, 82).

This aspect of oxytocin’s involvement illustrates two categories of its activities – an observable physiological factor and also an effect on less easily monitored mood aspects. This is an illustration that within the orbit of a particular behaviour, i.e. sexual responses, there is the opportunity for oxytocin to coordinate at least some of the diverse components of the biological activity.

In behaviours

As we have noted above, oxytocin, besides having effects which can be monitored biochemically, is also implicated in modulation of behaviours. Indeed the involvement of oxytocin acting as a neuropeptide in psychology has been the subject of several investigations (83).

Nevertheless the effects of administering oxytocin on behaviour is often modest. However oxytocin administration decreased fatigue, anger and anxiety (84) and vigour (85). Additionally oxytocin attenuated learning processes (85). The wide variety of observed effects has led to the suggestion that oxytocin has a general effect on cortical arousal rather than a specific effect limited to a certain stage of information processing (86). This view is not universally held. Oxytocin given intranasally to Vietnam veterans suffering from post-traumatic stress disorder reduced their response to combat imagery. The results were consistent with the predicted specific inhibitory effect of oxytocin on memory retrieval and conditioned responding rather than on non-specific arousal (87). The possibility that raised oxytocin levels during parturition altered cognition was investigated. The results suggested there was temporary impairing, although there was no correlation between oxytocin levels and cognitive performance (88). The evidence that oxytocin impairs some memory-related tasks has led to suggestions that it has a role in the forgetting of delivery pain in mothers. Oxytocin rises following ingestion of oral contraceptives, and a consequent effect on mental activities has been speculated (20). In addition levels of circulating oxytocin have a correlation with personality measures in women, although a causal relationship was not demonstrated. The correlation was weak, perhaps reflecting the broad spectrum of oxytocin action (89). A response to noise stress, resulting in an increase in oxytocin levels, was observed, but interestingly only in women with high emotionality reactivity (90). There is however a blood–brain barrier which makes such measurements of disputable value, since peripheral levels do not necessarily reflect levels at the pertinent neurones in the brain. Such a barrier can also act as a component in the regulation of responses to oxytocin by compartmentalising the potential targets (Table 1, J).

There have been several investigations of the role of oxytocin in children with obsessive-compulsive disorder (OCD), and some results suggest a subtype of OCD based on hypothalamo–neurohypophyseal dysfunction (91). Treatment with clomipramine improved symptoms in OCD children and increased oxytocin levels in the CSF (although the correlation of quantitative changes was

![Figure 3](https://example.com/figure3.png)

**Figure 3** Orgasm increases oxytocin levels. The effect of naloxone on plasma oxytocin levels at orgasm in eight healthy men. Values have been logarithmically transformed and are expressed as a percentage of the mean. B1, B2, baseline values; —— naloxone; - - - - saline. (From reference 136, reproduced with permission.)
bolites, and these different forms of oxytocin forms, N-alpha acetyl oxytocin, and oxytocin meta-forms of the peptide, e.g. COOH-terminal extended observed to increase FSH (105), although not all effect on LH (103, 104). In men oxytocin has been women under other conditions there was no detectable (sexual activity). When oxytocin was administered to between a physiology (ovulation) and a behaviour there is thus illustrated an oxytocin-mediated link period (102). This observation tempts speculation that women oxytocin advanced the luteinising hormone (100, 101). In animals (100, 101). The enzymes which catalyse the formation of the forms may contribute to modulation of biological activities (15). One form (a little larger than native oxytocin) is induced by oestrogen and detected in the peripheral circulation and observed in patients with end-stage renal failure, suggesting one reason for its detection might be related to lowered clearance (94).

The anterior pituitary gland
In addition to hypothalamic oxytocin following the well known neurosecretory pathway to the neurohypophysis there have been suggestions that some also reaches the anterior pituitary lobe via the hypothalamo–pituitary portal vasculature. Oxytocin is thus able to influence anterior pituitary hormones as a hypothalamic regulating factor.

ACTH
Regulation of ACTH by oxytocin and involvement in the stress response has been indicated from animal studies. In humans oxytocin seems to act reciprocally with vasopressin which is a stimulator of ACTH release. Oxytocin caused a dose–response reduction of ACTH in men (95). Stimulated responses have also been suppressed. Oxytocin reduced ACTH which was stimulated by insulin-induced hypoglycaemia, by vasopressin (96) or by CRH (97). Investigations in which ACTH rises were not sensitive to oxytocin have also been reported (98, 99).

Gonadotrophins
There are also several observations of oxytocin modifying gonadotrophin secretion in animals (100, 101). In women oxytocin advanced the luteinising hormone (LH) surge when administered in the preovulatory period (102). This observation tempes tincture that there is thus illustrated an oxytocin-mediated link between a physiology (ovulation) and a behaviour (sexual activity). When oxytocin was administered to women under other conditions there was no detectable effect on LH (103, 104). In men oxytocin has been observed to increase FSH (105), although not all investigators have noted such an effect (106).

Prolactin
Prolactin is often associated with oxytocin in lactation although there is little data indicating an endocrinological link in humans. In the human female oxytocin increased thyrotrophin-releasing hormone-induced prolactin release, but seems not to have a similar effect in the male (97).

In the case of tissues which have a changing constitution, such as the pituitary during the ovulatory cycle and the ovary in which cells are transformed from granulosal to luteal, then extra stage-dependent controls will be operative (Table 1, L) (107). The variation in population of cell types determines that the pituitary responses of LH and prolactin to oxytocin will not be consistent over all times.

A receptor can differentially couple to G-proteins depending on the characteristics, including the complement of second messengers, of the target cell (108, 109) (Table 1, M). Thus functional sequelae of activation of oxytocin receptors can be modified by the properties which arose from differentiation of the target cell.

The adrenal
Although oxytocin is believed to affect cortisol via ACTH, an adrenal site of oxytocin action has also been detected (110). Thus oxytocin is involved at not just one site in the integrated modulation of cortisol concentrations. The physiological modulation of stress is thus a complex network of endocrine control mechanisms, involving several hormones with oxytocin, one of the regulating hormones, being active at at least two sites. It is possible that this very complexity is a safeguard against an inappropriate adrenal response to a rise in oxytocin which was unrelated to a stress stimulus.

Composite regulatory elements which mediate tissue-specific expression (109, 111, 112) of target genes enable a stimulatory complex to include other components (besides oxytocin) to be present necessarily for an effect by oxytocin to be observed (Table 1, N). Thus for oxytocin activity to be manifest at any particular site, other components (e.g. growth factors, steroids) must act on the target too. These other factors will be controlled by processes specific to the target and so indirectly regulate oxytocin action, reducing the chance of inappropriate oxytocin-mediated effect.

Oxytocin has been detected also in the adrenal medulla (113).

The pancreas
There is also an oxytocin component in glycaemic control. Possibly oxytocin stimulates pancreatic A-cell secretion, enhances hepatic glucose and has a direct glycogenolytic effect. In addition oxytocin probably also increases insulin and glucagon (114) although apparently not under all circumstances (115). Oxytocin rises in hypoglycaemia and is modulated by glucocorticoids
The oxytocin rise in response to insulin is reduced in obese men. The oxytocin response to insulin was enhanced in obese but not normal men by the opioid antagonist naloxone, suggesting that there is abnormal activity of endogenous opioids in obese men (117) (Fig. 4). These results provide another illustration of the interactive nature of oxytocin-mediated biological systems, including in this case insulin and opioids together with oxytocin. There seems also to be sexual dimorphism in the regulation, such that although endogenous opioids modulate oxytocin release during insulin-induced hypoglycaemia in men, such is not the case in women (118). The oxytocin release in response to hypoglycaemia is exaggerated in patients with Type-I diabetes. It is possible that oxytocin might be involved in improving the impaired glucose counterregulation in these patients (119). The possibility of a paracrine role for oxytocin in the pancreas is suggested by the presence of the peptide in tissue (120).

It is worth noticing that a stimulus which elicits, from an oxytocin-producing unit, a specific physiological increase in oxytocin, at say the pancreas or ovary, does not lead to a similar response at all potential production sites. In considering control processes at a tissue level, it can be noted that examples of hormonally mediated responses are provided by cells of the granulosa and the pancreas which, in suitable circumstances, are activated to produce oxytocin. The regulation of receptors to these activating stimuli are responsive to local conditions. Thus oxytocin production is indirectly regulated by control mechanisms targeted to particular tissues. (Table 1, O). Oxytocin release is similarly modulated by local controls.

**Fat cells**

Oxytocin stimulates H$_2$O$_2$ generation in fat cells by a signal transduction mechanism. The H$_2$O$_2$ produced might participate in the regulation of fat cell differentiation and maintenance of the differentiated state (121). This activity of oxytocin on fat cells is a further reminder that oxytocin has a diverse range of targets, and a pathology which affects oxytocin has the potential to have a wide range of sequelae.

**Feeding**

There have been suggestions from animal studies that oxytocin affects appetite. Such a connection has not
been definitively established in humans. Oxytocin was not affected in a study in which normal subjects who consumed a large meal were administered cholecystokinin which slows gastric emptying and decreases food intake (122).

However in Prader–Willi syndrome (PWS), a disease characterised by insatiable hunger producing gross obesity, there is a reduction in important oxytocin neurones going to brain stem nuclei. There was a reduction in volume of the paraventricular nucleus (PVN), a reduction in total cell number in the PVN and a reduction in oxytocin neurones of the PVN (123) (Fig. 5). The results are consistent with oxytocin being a satiety hormone. Possibly a lack of peripheral oxytocin contributes to the diabetes mellitus and intolerance to glucose in PWS subjects. The reduced number of oxytocin neurones in PWS babies possibly partly explains the frequency of perinatal problems during delivery since there is suboptimal fetal oxytocin at labour (123).

In underweight women with restricting anorexia CSF oxytocin levels were low. It is speculated that the low levels might be a reflection of low food intake and thus the women have enhanced retention of cognitive distortion of the consequences of food intake. The perturbation in oxytocin may be significant in influencing the clinical symptoms including the behaviour associated with this condition (124). There is therefore a further example of an interaction between a biologically induced modulation and behavioural sequelae.

Pain perception

Among its activities oxytocin seems to reduce pain. Administration of oxytocin reduced back pains, probably via a mechanism involving opiates (125). It has also been noted that low oxytocin levels are present in children with recurrent abdominal pain. However a causal effect has not been demonstrated. In passing it is noted that children with recurrent abdominal pain are often anxious with increased muscular tension, and oxytocin apparently activates contrary effects (126); a connection between a physiology (pain) and a behaviour (anxiousness) noticed in a condition with a lack of oxytocin was thus postulated.

Oxytocin in non-basal states

Interactions of oxytocin-mediated systems have been recognised in speculations regarding clinical symptoms in some pathologies. In AIDS (127) and also in Parkinson’s disease (128) there are decreases in the PVN oxytocin-producing neurones which can possibly account for certain of the characteristics of patients. These can include impotence, occasionally observed increased appetite, and depression. In another area, as was noted above, alterations in secretion of oxytocin are believed to account for some of the symptoms associated with a subtype of OCD (129). There is also indirect evidence for oxytocin being involved in Alzheimer’s disease in which there is a selective degeneration of the basal nucleus of Meynert and changes in oxytocin levels in certain areas of brain and CSF (130, 131).

The role of oxytocin in depression is uncertain although perturbations have been reported. There was an increase in oxytocin immunoreactive neurones in the PVN of patients with symptoms of depression (132). On the other hand there was a reduction of plasma oxytocin concentration in another group of depressed patients (133).

The involvement of oxytocin in behavioural activities implies that certain pathologies will have behavioural corollaries. However as with physiological responses, it is likely that for a behavioural response, circumstances will modulate the effect of oxytocin at the cellular level to produce a greater or lesser effect. In fact the variability of experimental results between different studies has been assigned at least partly to the different conditions of the experiments (86). There is, however, uncertain information of the additional factors which modify the behavioural responses.

However not all side effects of oxytocin hypersecretion are unwelcome. It has been suggested that the sedation effects of breast feeding are due primarily to oxytocin, and this peptide might form the basis of an anti-stress treatment (134).

Conclusion

The review considered the relationship between the various activities of oxytocin and the manner in which
they are related in the body’s physiology. It is necessary to have some means of regulation so that there is not a tidal wave of oxytocin-initiated events whenever oxytocin is needed physiologically for a response. Those control mechanisms relating to oxytocin will also be applicable to a wide variety of other physiological systems, and so have a generality beyond those of this particular peptide. Some regulatory processes can modulate the responsivity to oxytocin. Other processes can modulate the production of oxytocin which occurs downstream from different physiological regulatory activation.

The investigation of oxytocin provides a general framework of study in which it can be noted that a peptide hormone can have several distinct actions, that the selective actions require differential modulatory mechanisms, and that the interrelationships between the actions result in sometimes unexpected effects.

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