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Oxytocin—its role in male reproduction and new potential therapeutic uses

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Oxytocin (OT) is traditionally thought of as a 'female' neurohypophysis hormone due to its role in parturition and milk ejection. However, OT is recognized as having endocrine and paracrine roles in male reproduction. At ejaculation, a burst of OT is released from the neurohypophysis into the systemic circulation and stimulates contractions of the reproductive tract aiding sperm release. There is conclusive evidence that OT is synthesized within the mammalian testis, epididymis and prostate and the presence of OT receptors (OTRs) through the reproductive tract supports a local action for this peptide. OT has a paracrine role in stimulating contractility of the seminiferous tubules, epididymis and the prostate gland. Interestingly, OT has also been shown to modulate androgen levels in these tissues via stimulation of the conversion of testosterone to dihydrotestostone (DHT) by 5α-reductase. The elucidation of OT's role in male reproduction has suggested a number of potential therapeutic uses for this hormone. Exogenous administration of OT has, in some cases, been shown to increase the numbers of ejaculated sperm, possibly by stimulating contractions of the reproductive tract and thus aiding sperm passage. Within the prostate, OT has been shown to affect gland growth both directly and via its interaction with androgen metabolism. Prostate pathologies due to unregulated cell proliferation/growth, such as benign prostatic hyperplasia and cancer, are unfortunately very common and few effective treatments are available. Greater understanding of paracrine growth mediators, such as OT, is likely to provide new mechanisms for treating such pathologies.

Key words: cell growth/male reproductive pathology/oxytocin/reproductive tract contractility/steroidogenesis

Introduction

Oxytocin (OT) and vasopressin (VP) are neurohypophysial hormones secreted by the hypothalamic magnocellular neurons and stored in the posterior pituitary until their release into the blood stream. They have similarities of structure, both being nonapeptides with a disulphide bridge between cystine residues 1 and 6. The OT family has a neutral amino acid, leucine at position 8, whereas the VP family has a basic amino acid, arginine at position 8. Isoleucine in position 3 is necessary for stimulation of OT receptors and Arginine or Lysine is essential to stimulate VP receptors.

OT and VP are synthesized as part of a prohormone that includes an oxytocin-neurophysin I (OT-NpI) and a vasopressin-neurophysin II (VP-NpII) (Zimmerman *et al*., 1974; Robinson, 1987) complex, respectively. For each hormone, the prohormone is packaged into neurosecretory granules and transported via axons to the posterior pituitary gland (Land *et al*., 1983; Robinson, 1987). OT and its carrier molecule NpI are stored in axon terminals located in the posterior pituitary until their release into the blood stream (Renaud and Bourque, 1991). OT and NpI are found in high concentration in the neurosecretory granules of the posterior pituitary in a 1:1 ratio. NpI targets, packages and stores OT within the granules before release into the blood stream (Gimpl and Fahrenholz, 2001).

In the human, the OT and VP genes are similar in their intron–exon structure and are present on the same chromosomal locus but transcribed in opposite directions (Sausville *et al*., 1985; Mohr *et al*., 1988). The human OT-NP I gene is located on chromosome 20p13 (Rao *et al*., 1992). In rats, the OT gene has been shown to consist of three exons encoding a preprohormone that is processed to the two mature peptides including OT. The first exon (A) comprises the non-coding 5′ promoter region, a putative signal peptide, the nonapeptide OT and the NH_2-terminal region of NpI. The second exon (B) encodes the central conserved region of NpI and the third exon (C) encodes the COOH terminal of NpI and an arginine residue at the end (Ivell and Richter, 1984). The central part of exon B, except for a single base change, is similar to the equivalent part of the VP gene and confirms a common ancestral origin (Ivell and Richter, 1984). However, the promoter sequences on exon A of the two genes are distinct, reflecting the differing functions and regulation of the two hormones (Ivell and Richter, 1984).

The similarity in their structures but the difference in polarity probably enables OT and VP to interact with their respective receptors (Barberis *et al*., 1998). The OT receptor (OTR) has only approximately 10-fold higher affinity for OT compared to VP. VP acts as a partial agonist to the OTR. However, to elicit the same response as OT, the concentration of VP needs to be approximately 100-fold (Chini *et al*., 1996).

Almost all vertebrates possess OT-like and VP-like peptides. Two evolutionary lineages have been proposed—an isotocin-mesotocin-oxytocin line that is associated with reproductive functions and a vasotocin–VP line associated with water homeostasis (Acher and Chauvet, 1995).

OT has been traditionally recognized as a 'female' hormone involved in parturition and milk ejection. The pregnant uterus is an important target organ for OT, which is a potent uterotonic and is used clinically for induction of labour. However, despite the use of very sensitive assays, many researchers have failed to show an increase in OT during pregnancy or early labour (Mitchell *et al*., 1998) questioning the physiological role of OT in the initiation of labour (Chard, 1989; Nishimori *et al*., 1996). Women with known posterior pituitary dysfunction can go through normal labour (Chard, 1989) and in OT knockout mice (OTKO) it has been shown that OT is essential for milk ejection but is not essential for normal fertility or reproduction including parturition (Nishimori *et al*., 1996).

Presence of OT mRNA and OTRs has conclusively proven that OT is not only synthesized locally in a number of female reproductive organs but also acts as a paracrine factor in the female reproductive tract (reviewed in Gimpl and Fahrenholz, 2001). OT action may be direct, through the activation of myosin light chain kinase (Phaneuf *et al*., 1993) or indirect by stimulating the synthesis of prostaglandin $F_{2\alpha}$ (Fuchs *et al*., 1981). The paracrine role of OT in luteal regression has been studied in sheep ovaries (McCracken *et al*., 1999). This has raised questions regarding the role of OT in male reproduction. Does OT have any function in male reproduction?

The aim of this article is to summarize our current knowledge regarding the endocrine and paracrine roles of OT in male reproduction and discuss the potential future clinical applications of this hormone.

OT and sexual behaviour in the male

Penile erection is one of the most important sexual responses and its achievement is essential for successful reproduction. Different neural and/or endocrine mechanisms are known to regulate penile erection. OT is one of the most potent agents known to induce penile erection and, in the rat, nitric oxide (NO) has been shown to be the key mediator of its actions (Argiolas, 1992). OT neurons within the paraventricular nucleus (PVN) that project to extrahypothalamic areas of the brain and spinal cord are involved in this effect (Melis *et al*., 1986).

Yanagimoto *et al*. (1996) have demonstrated that electrical stimulation of the dorsal penile nerve and tactile stimulation of the glans penis elicits a specific activation of 40–50% of oxytocinergic neurons in the PVN of the hypothalamus. Their study suggests that somatosensory information from the penis is transmitted to the PVN through the dorsal penile nerve. This afferent stimulus results in activation of oxytocinergic neurons in the PVN leading to the release of hypothalamic OT at ejaculation establishing an OT-based reflex arc in the male similar to the Fergusson reflex or the milk let-down reflex seen in the female.

In several animals including the human male, a pulse of OT probably of hypothalamic origin is associated with ejaculation (Ogawa *et al*., 1980; Carmichael *et al*., 1987; Murphy *et al*., 1987). It may be that the systemic pulse of OT at ejaculation is accompanied by a central effect of OT on sexual behaviour.

Studies of male rat sexual behaviour indicate that OT not only facilitates ex copula penile responses but also contributes to post-ejaculatory refractoriness (Bitran and Hull, 1987; Hughes *et al*., 1987). In the rat, OT has been shown to reduce the number of intromissions before ejaculation, increase the latent period of first mount and intromission and to lengthen the post-ejaculatory refractory period (Stoneham *et al*., 1985; Hughes *et al*., 1987). The concentration of OT in the cerebrospinal fluid (CSF) doubles 5 min after ejaculation and increases to three times the basal levels 20 min after ejaculation. This rise in CSF OT at ejaculation is abolished by discrete electrolytic lesions to the lateral and posterior paraventricular parvocellular nuclei (Hughes *et al*., 1987).

The intensity of orgasm in both men and women has also been found to correlate with plasma OT levels (Carmichael *et al*., 1994). In men, the rise in systemic OT at ejaculation could be suppressed by naloxone, an opioid antagonist possibly acting on the opioid receptors in the posterior pituitary (Murphy *et al*., 1990). This suggests that the ejaculatory OT may be derived from the magnocellular neurons of the hypothalamo-pituitary system. Suppression of the systemic OT pulse has not been found to inhibit ejaculation indicating that ejaculation is not controlled by OT (Marshall *et al*., 1996). However, male human volunteers reported a feeling of decreased arousal and pleasure at orgasm on suppression of the systemic OT pulse by naloxone (Murphy *et al*., 1990). This suggests that the release of OT at ejaculation may also play a role in sexual satiety. Although OT may not directly affect ejaculation, it may have a central effect along with acting on the peripheral genitalia.

Serotonin receptor agonists have been shown to produce an increase in OT (Uvnas-Moberg *et al*., 1996) and selective serotonin reuptake inhibitors (SSRI), used for treatment of depression have been known to progressively inhibit orgasm and induce a transient decrease in libido in a time- and dose-dependent fashion (Cantor *et al*., 1999). Treatment with OT restores the ejaculatory response but has no effect on the intensity of sexual excitement indicating that SSRIs probably suppress ejaculatory responses by interrupting the action of OT.

In contrast to the findings of a facilitatory role of OT on sexual behaviour in male rats, in the male prairie vole, OT causes an immediate cessation of all sexual activity which continues to remain so for at least 24 h (Mahalati *et al*., 1991).

Local production of OT in the male reproductive tract

The first indication of local OT synthesis within the male reproductive tract was obtained by Nicholson *et al*. in 1984. Using radio-immunoassay (RIA) and high-performance liquid chromatography (HPLC) an OT-like peptide was detected in both the human and rat testis. The co-localization of neurophysin with this OT-like peptide, together with the higher than plasma concentrations recorded, pointed towards local synthesis (Nicholson *et al*., 1984). The development of techniques to identify specific mRNA transcripts have since provided conclusive evidence to

support the local synthesis of OT within a number of reproductive tissues in the male tract from a range of species (summarized in Table I).

OT receptors and their localization in the male reproductive tract

The OTR is a seven transmembrane-domain polypeptide belonging to the rhodopsin-type class 1 G-protein coupled receptor (GPCR) family (Kimura *et al*., 1992). Classically, OTRs are coupled to $G_{q/11}\alpha$ class GTP binding proteins that stimulate the activity of phospholipase C-β isoforms along with Gβγ (Ku *et al*., 1995). This leads to generation of inositol tri-phosphate (ITP) and 1,2-diacyl glycerol (DAG). ITP triggers release of intracellular calcium (Ca^{2+}) which in turn triggers a variety of cellular events (Gimpl and Fahrenholz, 2001 and the references contained therein). In smooth muscle cells such as the myometrium, the calcium–calmodulin complex triggers the activation of MLCK which initiates smooth muscle contraction (Sanborn *et al*., 1998). Like other GPCRs, the OTR undergoes rapid homologous desensitization following agonist stimulation. More than 60% of the human OTRs are internalized within 5–10 min of agonist stimulation (Gimpl and Fahrenholz, 2001). After agonist addition and activation, the OTR binds with β-arrestin following which the OTRs are targeted into clathrin-coated pits for internalization (Oakley *et al*., 2001). About 10–15% of OTRs are localized in caveolae-like cholesterol-rich membrane microdomains (Gimpl and Fahrenholz, 2000). The OTR-caveolin complex is not recycled back to the cell surface (Gimpl and Fahrenholz, 2000) but remains confined to the plasma membrane after exposure to ligand. The change in localization of the OTR induces a change in its mitogenic potential and promotes cell proliferation (Guzzi *et al*., 2002).

For OT to be accepted as a key paracrine regulator of male reproductive function, a pre-requisite is the presence of specific receptors within these tissues. OTR's have been identified and localized within tissues of the reproductive tract, although a degree of species variation is evident (Table I).

Table I. Summary of published evidence providing evidence for oxytocin synthesis (mRNA, neurophysin) and oxytocin receptors (mRNA, protein localization) in tissues of the male reproductive tract

		Evidence for presence of	
Tissue	Species	Oxytocin synthesis	Oxytocin receptor
Testis	Human	+ (Ivell *et al*., 1990, 1997)	+ (Frayne and Nicholson, 1998)
	Marmoset	+ (Einspanier and Ivell, 1997)	+ (Einspanier and Ivell, 1997)
	Macaque		+ (Frayne and Nicholson, 1998)
	Rat	+ (Foo *et al*., 1991; Nicholson and Hardy, 1992)	+ (Frayne and Nicholson, 1995; Bathgate and Sernia, 1994)
	Pig		+ (Maggi *et al*., 1987)
	Sheep	+ (Ungefroren *et al*., 1994; Assinder *et al*., 2000)	+ (Whittington *et al*., 2001)
	Cow	+ (Ang *et al*., 1991; Ungefroren *et al*., 1994)	
	Wallaby		– (Parry and Bathgate, 1998)
Epididymis	Human	+ (Filippi *et al*., 2002b)	+ (Filippi *et al*., 2002b)
	Marmoset	(+) (Einspanier and Ivell, 1997)	(+) (Einspanier and Ivell, 1997)
	Macaque		+ (Frayne and Nicholson, 1998)
	Rat	+ (Harris *et al*., 1996)	
	Pig		+ (Maggi *et al*., 1987)
	Sheep	+ (Assinder *et al*., 2000) – (Knickerbocker *et al*., 1988; Veeramachaneni and Amann,1990)	+ (Whittington *et al*., 2001)
	Cow		
	Wallaby		+ (Parry and Bathgate, 1998)
Prostate	Human	+ (Whittington *et al*., 2004)	+ (Frayne and Nicholson, 1998; Whittington *et al*., 2004)
	Marmoset	– (Einspanier and Ivell, 1997)	+ (Einspanier and Ivell, 1997)
	Macaque		+ (Frayne and Nicholson, 1998)
	Rat		+ (Assinder *et al*., 2004)
	Pig		
	Sheep		
	Cow		
	Wallaby		+ (Parry and Bathgate, 1998)
Penis			
	Human		+ (Vignozzi *et al*., 2005)
	Marmoset		
	Macaque		
	Rat		+ (Zhang *et al*., 2005)
	Pig		
	Sheep		
	Cow		
	Rabbit		+ (Vignozzi *et al*., 2004)

+, Detected; (+), weak detection; –, not detected.

Physiological roles for OT in the male reproductive tract

OT and tract contractility

From established studies in the female OT is considered a 'myotonic' hormone—causing contractions of the uterine muscle and the myoepithelial cells of the breast. Spermatozoa are not able to display their motility within the male tract and hence need to be transported from the testis following spermiation. In the epididymis, spermatozoa undergo maturation and can be stored, for extended periods of time in some species, until their release into the ductus deferens at ejaculation. OT has been postulated to modulate contractility of the male tract to regulate sperm transport and maturation (Figure 1).

OT and seminiferous tubule contractility

Spermatogenesis is an organized process occurring in an ordered fashion and in the rat comprises of 14 histologically distinct stages arranged linearly along the seminiferous tubule. Non-motile spermatozoa are shed from the seminiferous epithelium in a process called 'spermiation' at the end of stage VIII and are transported through the lumen of the tubule to the rete testis. This transport is mediated by contractions of the myoid cells surrounding the seminiferous tubules (Hargrove *et al*., 1977). Since the early nineteen fifties, it has been known that seminiferous tubules are spontaneously contractile (Roosen-Runge, 1951). Two types of tubular contractility—type A and type B (Worley and Leendertz, 1988) have been described. Type A movements are high frequency movements, like ripples of the tubule walls, whereas type B movements are large contractions, involving whole sections of the tubule and are associated with bulk movements of the seminal contents and transporting spermatozoa from the testis. Type B movements occur much less frequently compared to type A movements (Worley *et al*., 1985). Niemi and Kormano (1965) were the first to show that tubule contractility can be increased, *in vitro*, by the addition of OT to the bathing fluid. This was confirmed by Worley *et al*. in 1985 who illustrated that both the types of tubule movement are enhanced by the addition of even small amounts of OT (1 ng/ml), or VP, to the perfusing fluid.

The function of type A movements is unclear, but they may be associated with sperm shedding at spermatogenic stage VIII. Indirect evidence supporting this arises from evidence that seminiferous tubules of neonatal rats are quiescent, and OT is absent, until day 8 post-natally. Only with the onset of spermatogenesis is increasing seminiferous tubule contractility detected (Worley *et al*., 1985). Adult male rats devoid of Leydig cells due to ethane dimethane sulphonate (EDS) treatment have undetectable amounts of OT and significantly reduced seminiferous tubular activity *in vitro*. However, 4 weeks after treatment immunoassayable OT returns, together with the re-appearance of Leydig cells and

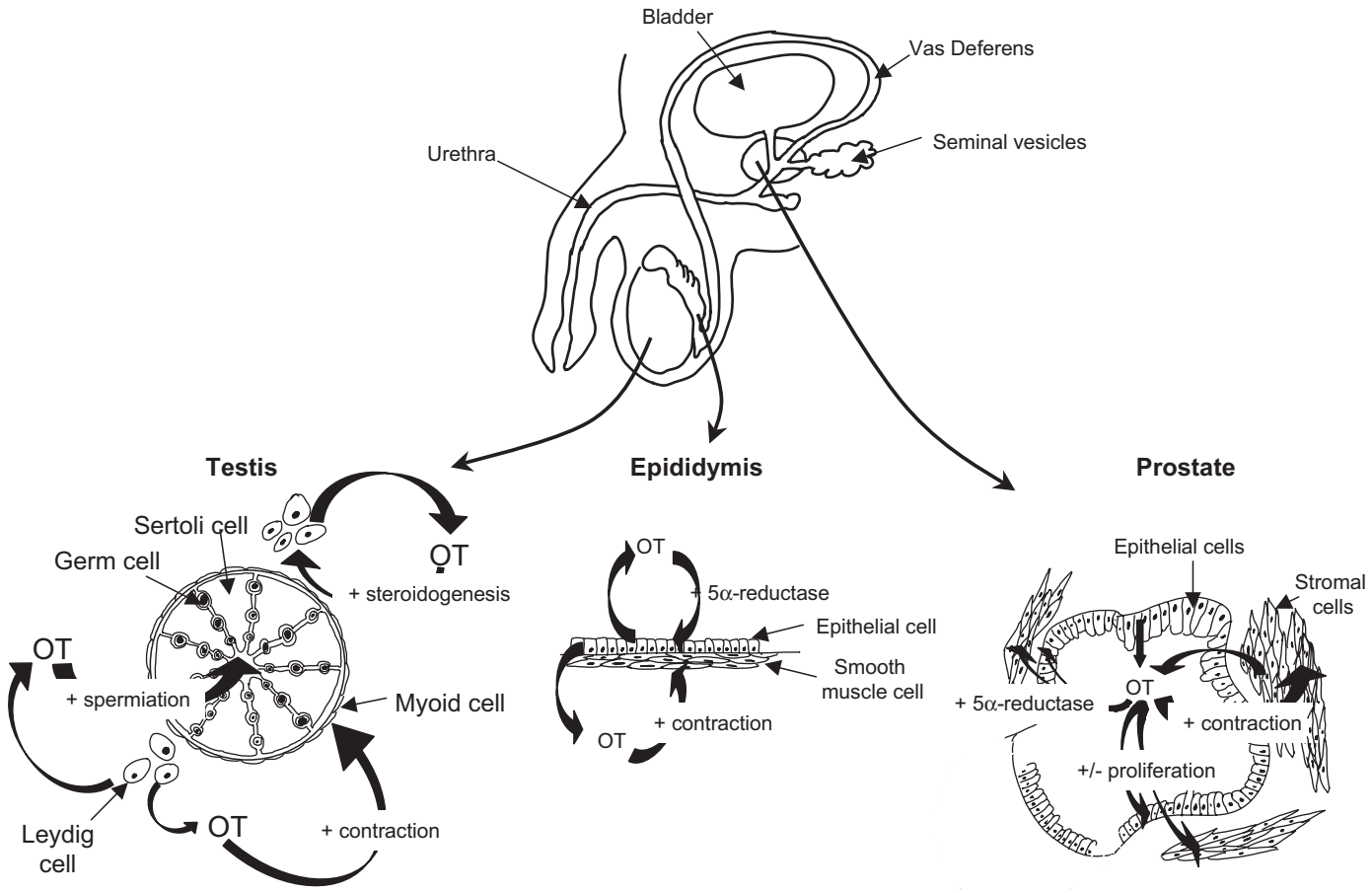

Figure 1. Overview of the paracrine/autocrine functions of oxytocin within the male reproductive tract.

restoration of normal tubular activity (Nicholson *et al*., 1987). Computer analysis and time-lapse videomicrography experiments provided direct evidence confirming OT's role in tubule contractions (Harris and Nicholson, 1998a,b). Contractility of rat seminiferous tubules *in vitro* depends on the stage of the spermatogenic cycle. Mean basal contractility is significantly lower at stages VII–VIII than that observed in stages IV–V and XIII–I. However, the addition of OT produces a large increase in contractile activity in tubules at stages VII–VIII, whereas no effect is seen on those at stages IV–V. As spermiation occurs at stage VIII, the effect of OT at this time suggests that it may be important in co-ordinating the movement of the developing spermatozoa into the tubular lumen (Harris and Nicholson, 1998a).

The *in vitro* evidence supporting a role for OT in spermiation and testicular sperm transport has been corroborated with *in vivo* studies in a number of species. In pre-pubertal rats, it takes approximately 45 days for spermatozoa to appear in the epididymis. Subcutaneous injection of OT daily from post-partum day 40 in pre-pubertal male Wistar rats advances the arrival of spermatozoa into the epididymis by a day compared to control animals. In contrast, daily injection of an OT antagonist (OTA) delays this arrival by a day (Frayne *et al*., 1996). The sperm count in the epididymis was significantly higher at all times, and spermiation was also advanced by a day in OT-treated rats compared to controls. Both, the earlier spermiation and appearance of spermatozoa in the epididymis in OT-treated rats suggests that OT may have a direct effect on seminiferous tubule contractility in pre-pubertal rats, and these events may not solely be due to a change in rate of fluid transport.

Assinder *et al*. (2002) demonstrated in pubertal transgenic mice that overexpress the bovine OT gene (bOT4.2) sperm are shed earlier than wild-type mice. Conversely, in OTKO, shedding of sperm in the first spermatogenic wave is delayed but not completely prevented (Assinder *et al*., 2002). The fact that the appearance of residual bodies in OTKO mice was delayed but not absent altogether suggests that OT is only one of the factors responsible for spermiation and sperm transfer in the mouse.

Whittington *et al*. (2001) investigated whether OT increases sperm movement in the ram testis *in vivo*. Injection of OT into the testicular artery increased the concentration of spermatozoa in the rete testis fluid (Whittington *et al*., 2001). Treatment with OTA inhibited this response, thus indicating that the effect was specifically dependent on OT. This could reflect an increase in the rate of the transport of spermatozoa or an increase in the number of spermatozoa shed from the seminiferous epithelium.

Although the above studies suggest a direct association between OT, spermiation, seminiferous tubule contractility and subsequent sperm transfer to the epididymis, the exact mechanism of action is not clearly understood. If OT has a direct action on tubule contractility, then OTRs would be expected to be localized to the myoid cells that encircle each seminiferous tubule. This has not been shown to be the case (Einspanier and Ivell, 1997; Frayne and Nicholson, 1998; Whittington *et al*., 2001). Although this may be due to inadequacies of present staining techniques, an alternative explanation is that OT may not act via its own receptors but may instead act via the VP receptor, V_{1a}. Northern blot analysis on primary cultures of purified myoid cells from post-pubertal rats has demonstrated the expression of V_{1a} receptors (Howl *et al*., 1995). Harris and Nicholson (1998b) also confirm the presence of biologically active V_{1a} receptors in rat testis. In support of this explanation is the fact that OT is known to be an agonist at V_{1a} receptors *in vivo*, albeit with a lower affinity than for OTR. However, the addition of a VP agonist into the culture medium did not have any effect on the OT-stimulated rise in tubular contractility (Harris and Nicholson, 1998b). This suggests that the action of OT on seminiferous tubule contractility is mediated by a route independent of VP.

A second, more likely, explanation is that the response to OT is mediated indirectly via factors released from other cells within the seminiferous tubules such as the Sertoli cells. The presence of OTRs on Sertoli cells has been confirmed in a number of species including both the marmoset monkey (Einspanier and Ivell, 1997) and the human (Frayne and Nicholson, 1998). This would explain why such small quantities of OT are sufficient to stimulate seminiferous tubule contractility. The spermatogenic wave arrangement of spermatogenesis in many of the species means that adjacent sections of the tubules are at different stages of the cycle and therefore have different hormonal requirements. Hence, there is a need for complex communication to occur between the various testicular compartments and cell types. Pickering *et al*. (1990) attempted to draw together the various complex interactions taking place between different cell types within the testis and the place of OT in this. However, an understanding of the role of OT in steroidogenesis is essential to understand it in more detail. We will hence return to the hypothesis put forward by Pickering *et al*., (1990) after discussing the role of OT in steroidogenesis in the male.

OT and epididymal contractility

It is widely recognized that the epididymis has multiple functions ranging from sperm maturation to storage (see Moore, 1995). Contractility of the epididymis is important for the movement and maturation of sperm. It is apparent that the epididymis exhibits a basal contractility that can be modified by a variety of agents, including OT.

Hib (1974) demonstrated for the first time that, in the mouse, OT increases cauda epididymal contractility *in vitro* suggesting that OT may have a role in the propulsion of sperm from the cauda to the vas deferens at ejaculation. When the contractility of the mouse epididymis was recorded *in vivo*, OT produced a progressive increase in the amplitude and frequency of the contractions as well as the tone of the epididymal tubule (Hib, 1977).

OT has been shown to alleviate the reductions in the frequency, weight and sperm content of spontaneous rat ejaculates following copulation (Ågmo *et al*., 1978). Presumably, by stimulating epididymal contractility, OT shortens the time after copulation during which the epididymal sperm reserves are reduced. Studdard *et al*. (2002) studied the effects of various concentrations of OT and VP on the frequency and extent of contractions of the caput epididymis and on the resting tone of the epididymis as measured by a change in the resting diameter of the epididymis in the rat. By using videomicrography, they observed that contractions in the caput epididymis are peristaltic in nature and always progress in one direction from the caput to the cauda. Movement of the luminal contents was bidirectional, but the net effect was always towards the distal end (Studdard *et al*., 2002). *In vitro* addition of OT solutions at concentrations of 10^{-12}–10^{-7} M significantly increased the frequency of contractions with no significant change seen in the resting tubule diameter. However, as the concentration of OT increased, the diameter of the tubules decreased at the end

of contractions with an apparent plateau effect at 10^{-11} M, indicating larger contractions with lower OT concentrations in comparison with the control group (Studdard *et al*., 2002). The bimodal response of the intensity of contractions to OT may be either due to receptor saturation followed by cross reactivity with other receptors at higher concentrations or related to activation of another signal transduction pathway at higher peptide levels. These effects of OT *in vitro* suggest that it may have a role in regulating epididymal contractility and sperm transport.

Knight (1974) showed that in the ram, OT has a summative effect on epididymal contractions when administered with adrenaline. Adrenergic blocking drugs inhibited the adrenaline-stimulated contractions but had no effect on OT-induced contractions (Knight, 1974). OT has also been shown *in vivo* to have a specific action on the ram epididymis and increase sperm transport (Nicholson *et al*., 1999). OT (10 and 100 μg) significantly increased both fluid output and the number of spermatozoa in the luminal fluid of the cauda epididymis within 10 min of treatment, and the effect was dose dependent (Nicholson *et al*., 1999). Treatment with OTA significantly reduced the fluid output and spermatozoal numbers whilst pre-treatment with OTA inhibited the stimulatory effects of OT indicating that OT acts on epididymal contractility through its own cognate receptor (Nicholson *et al*., 1999). This stimulatory effect suggests that OT affects epididymal contractility directly leading to a significant increase in the transport of spermatozoa into the vas deferens and the ejaculate.

In the rabbit, it has been shown by *in vitro* cultures of the epididymal epithelial cells that OT induces the release of another potent stimulator of epididymal contractility, endothelin-1 (ET-1) which may be involved in amplifying OT-induced contractility (Filippi *et al*., 2002a). Blocking ET-1 signalling with a specific antagonist significantly reduced the contractile effect of OT (Filippi *et al*., 2002a). In the human epididymis, OTRs have been localized to smooth muscle and the epithelial cells indicating that OT may have a similar role in regulating human epididymal contractility, and hence, sperm progression through the genital tract as has been shown in animal studies (Frayne and Nicholson, 1998). A recent study by Filippi *et al*. (2005) in both the rabbit and human has illustrated that the synergism between OT and ET-1 on epididymal contractility is estrogen dependent (Filippi *et al*., 2005).

OT and prostate contractility

OT, VP and vasotocin have been shown to increase the resting tone of the prostate in the guinea pig, rat, dog and man and also increase contractile activity *in vitro* (Bodanszky *et al*., 1992). In fact, OT was found to be a more potent inducer of contractile activity than adrenergic agonists (Caine *et al*., 1975). This suggests that OT may be involved in both maintaining prostatic tone and in the co-ordinated contractions of the prostate at ejaculation.

OT and penile contractility

OT has been shown to be one of the most potent agents known to induce penile erection. However, the significance of OT in the control of sexual arousal and penile erection in man has been elucidated only recently. Levels of OT measured in the penile blood of healthy males under different penile conditions (flaccidity, tumescence, rigidity and detumescence) have shown that mean OT plasma levels in the systemic and corpus cavernosus blood increased when the flaccid penis became tumescent. The levels increased even further from tumescence to rigidity in the cavernous blood but were unaltered in the systemic blood. However, during detumescence, the OT levels in the cavernous blood decreased, whereas those in the systemic blood increased. This indicates that OT plays an important role in male sexual arousal and penile erection (Uckert *et al*., 2003). The developing penis in the fetus has been shown to express a very high level of OTR mRNA. The OTR protein is also highly expressed and immunolocalized both in the mesenchymal body and in the surrounding blood capillaries, which will later constitute penile trabeculae and sinusoids. *In vitro* studies on cultured human smooth muscle penile cells have demonstrated the presence of specific OTR with a high affinity for OT and OTA (Vignozzi *et al*., 2005). RT–PCR and Northern blot have confirmed the presence of OTRmRNA and mature OTR protein has been detected in the rabbit and human corpus cavernosum (CC). OTR was immunolocalized to the endothelial and smooth muscle compartments of cavernous spaces and blood vessels. OTR receptor density in the penis is similar to that seen in other portions of the male genital tract. OT's effects on contractility may be mediated via estrogens (Vignozzi *et al*., 2004). *In vivo* studies have also confirmed that OTR regulates penile detumescence in the rat (Zhang *et al*., 2005). Penile expression of OTR and OTRmRNA has been shown to be comparable to that observed in testis and prostate. *In vivo*, intra-cavernous injection of OT inhibited the increase in intracavernous pressure (ICP) in a dose-dependent manner This effect was further shown to be counteracted by the OTR antagonist, atosiban, both *in vitro* and *in vivo* (Zhang *et al*., 2005).

OT and steroidogenesis

The synthesis of OT by the Leydig cell together with the presence of OTR's on this cell type suggests that OT may have a role in the modulation of testicular steroidogenesis. However, the data in this area is confusing. Adashi and Hsueh (1981) established that arginine vasopressin (AVP) and related neurohypophysial hormones exerted direct inhibition of testicular androgen biosynthesis *in vitro*. They showed that OT inhibits gonadotropin-stimulated androgen biosynthesis in isolated rat Leydig cells via testicular recognition sites similar to those mediating the pressor actions of the neurohypophysial hormones. Using capillary gas chromatographic steroid profiling, Kwan and Gower (1988) reported that OT completely inhibited androgen biosynthesis and abolished the formation of all C21 and C19 metabolites of pregnenolone.

Although part of a study by Nicholson *et al*. (1991) agreed with these results by showing that *in vivo* long-term administration of OT to the adult rat testis resulted in a significant reduction of testicular and plasma testosterone (T) levels throughout the 4 week study period, the decline in testosterone concentrations was not accompanied by alterations in spermatogenesis or epididymal sperm counts. This study also demonstrated a concomitant increase in both plasma and testicular levels of dihydrotestostone (DHT) with OT treatment. These data suggested that OT could influence the conversion of testosterone (T) to DHT, which may explain why there was no effect on spermatogenesis with continuous administration of intra-testicular OT (Nicholson *et al*., 1991).

Tahri-Joutei and Pointis (1988) studied the dose and time effects of OT treatment on basal and HCG-stimulated T accumulation by purified mouse Leydig cells in primary culture. After pre-treatment

of Leydig cells with OT (10^{-6} M) for 24 h, stimulation of acute basal (3 h) T accumulation was noted. The stimulation was both dose and time dependent, and the effectiveness was more pronounced at puberty indicating that acute treatment with OT may have a stimulatory effect on testicular androgen synthesis.

The bovine OT gene has been expressed in the testes of two independent transgenic mouse lines. Analysis with HPLC showed that transgenic mice testis overexpresses OT by almost 10-fold and their levels of intratesticular T and DHT are significantly lower. However, there appears to be no detectable effect of this overproduction of OT on testicular morphology or fertility parameters. This points to a local, paracrine role for OT in the modulation of Leydig cell function (Ang *et al*., 1994). These results are in contrast to those reported by Tahri-Joutei and Pointis (1988) where short-term exposure of cultured Leydig cells to OT increased basal T levels in normal wild mice. Sharpe and Cooper (1987) compared the effects of four hormones (OT, VP, opiates and GnRH) on purified adult rat Leydig cells under various conditions *in vitro* and *in vivo*. They noted that OT had no effect on T production in either experimental scenario.

Frayne and Nicholson (1995) re-evaluated the effects of OT and VP on testicular steroidogenesis by use of short-term exposure (<10 h) of isolated adult rat Leydig cells to OT, VP, OT agonist and OTA (antagonist). OT (10^{-9}–10^{-5} M) significantly increased the basal T production in a dose-dependent manner but had no effect on LH-stimulated T production. An OT agonist (TGOT[Thr4, Gly7]-OT) also induced a dose-dependent increase in basal T production. This effect was specific and was inhibited by the use of an OTA suggesting that the effects of OT on testicular T production are mediated via specific OTR's. In contrast to this, the effect of VP on basal T production was inconsistent and appeared to significantly decrease the LH-stimulated production of T.

Gerendai and Csernus (1995) studied the effect of intratesticular administration of OT on testicular steroidogenesis in immature rats, 5–9 and 25 days old. Intratesticular injection of OT (20, 50 and 200 ng) in one testis with contralateral orchidectomy resulted in a significant increase in basal T production *in vitro* and increased serum T concentration *in vivo*, indicating that testicular OT in immature rats may act as a local stimulator of T.

An effect of OT on testicular steroidogenesis has also been seen in goat testis *in vitro* (Inaba *et al*., 1999). Exposure of goat testis to OT (100 nM) for 6 h led to a 3.5-fold increase in DHT with a simultaneous decrease in T, again suggesting that OT can modulate the conversion of T to DHT. When these data are taken together, it appears that acute administration of OT stimulates testosterone production, particularly in young animals, whilst more prolonged exposure to OT results in a decline in testosterone concentrations but an increase in DHT production. However, it must also be considered that any increase in androgen production after OT administration is due to OT exerting an action at a pituitary level. Evans *et al*. (1999) showed that *in vitro* OT increased the LH secretory capabilities of pituitary gonadotrophes.

The presence of more intense staining of OTRs on the Sertoli cells than in the Leydig cells of the ram testis (Whittington *et al*., 2001) may provide indirect evidence supporting this peptide's role in the regulation of steroidogenesis as this cell type is the main site of the enzyme 5α reductase that irreversibly converts T to DHT.

OT has been shown to increase 5α -reductase activity in the testis and epididymis of adult male rats (Nicholson and Jenkin, 1994). *In vitro* experimentation demonstrated that OT increased 5α -reductase activity in a dose-related manner. Pickering *et al*. (1990) postulated that 'a group of Sertoli cells sense that the particular stage of the spermatogenic cycle taking place in their immediate environment needs cell re-arrangement or a decrease in local androgen production. By secreting a factor that leads to a release of OT from the neighbouring Leydig cells, the Sertoli cells can bring about a decrease in local T production as well as cause a local increase in the undulating type A movements of that section of the tubule'. In this way, the physiological actions of OT on seminiferous tract contractility and steroidogenesis can be explained logically and the origin of OT does not affect this hypothesis (Pickering *et al*., 1990).

Androgens, especially DHT, are necessary for epididymal function, and the presence of OT and OTRs in the epididymis indicate that OT may also have a similar role in epididymal function.

In the prostate, OT has been shown to stimulate the conversion of T to DHT by stimulating the activity of the enzyme 5α reductase (Nicholson, 1996). The alterations in 5α-reductase activity probably reflect both a direct action on the enzyme and a stimulation of enzyme synthesis (Assinder *et al*., 2004). However, in adult rats, prolonged administration of OT results in only a transient increase in DHT and 5a-reductase activity. Local concentrations of OT in the prostate are negatively regulated by androgens and possibly also by estrogens in the rat (Nicholson and Jenkin, 1995). In contrast to this, in the dog and human prostate, OT concentrations are positively correlated with androgens indicating species differences in the local feedback mechanisms that regulate OT and its interaction with androgens.

OT and cell growth/proliferation

The development and growth of the prostate gland in all species is dependent upon androgens. The human prostate is unusual, in that as men age prostate growth often becomes de-regulated resulting in either benign or malignant overgrowth. DHT has been shown to be an important factor in the pathogenesis of benign prostate hyperplasia (BPH) (Luke and Coffey, 1994) and prostatic carcinoma (Abrahamsson, 1999). However, failure of anti-androgen treatments to completely halt the progress of prostatic hypertrophy and neoplasia suggests that other paracrine/autocrine factors may also be involved in the regulation of prostatic growth. OT has been postulated to regulate growth of the prostate (Nicholson, 1996) and to be involved in the pathogenesis of prostate disorders.

OT has been shown to modulate mitotic activity in various organs including bone osteoblasts (Petersson *et al*., 2002), the breast (Bussolati *et al*., 1996), ovary (Morita *et al*., 2004) and small cell lung cancer cells (Pequeux *et al*., 2002). The effects of OT on cellular proliferation are tissue specific. Whereas in osteoblasts and human small cell carcinoma of the lung, OT stimulates growth (Pequeux *et al*., 2002), in human breast cancer cells (Cassoni *et al*., 1994) and ovarian carcinoma cells (Morita *et al*., 2004), OT inhibits cellular proliferation. OT inhibits proliferation of MCF7 estrogen-dependent human breast carcinoma cells via the OTR and has also been shown to modulate the expression of ERα both at mRNA and protein level (Cassoni *et al*., 2002). OTR expression has been demonstrated in ovarian carcinoma tissues, and OT has been shown to inhibit not only proliferation but also migration and invasion of ovarian carcinoma cells both *in vitro* and *in vivo*

(Morita *et al*., 2004). However, the exact mechanism of action of OT in ovarian carcinoma cells is not known.

An OT-like peptide and OTR have been localized to the prostate of the dog, rat, possum (Fink *et al*., 2005) and man (Whittington *et al*., 2004). Both proteins are localized mainly in the acinar epithelial cells. OTRs have also been localized to the stromal cells of the prostate in human and macaque monkey (Frayne and Nicholson, 1998) and also to the basal cells of the secretory epithelium of the marmoset prostate (Einspanier and Ivell, 1997). The fact that the concentration of OT is far higher in the prostate than in the plasma and OT mRNA has been localized in the human prostate suggests that OT may be synthesized locally in the prostate (Nicholson and Jenkin, 1995).

OT was observed to increase the size of accessory sex glands in T-supplemented, castrated rats (Debackere *et al*., 1961) and in the rabbit prostate, increased the height of the epithelial cells (Armstrong and Hansel, 1958). Mitogenic effects of OT have been observed in the rat prostate of animals with either low gonadotrophin levels or after castration where OT attenuated post-castration prostatic atrophy (Popovic *et al*., 1982). The volume of the prostate, the epithelial cell volume and the diameter of the acinar lumens were all seen to increase significantly following daily administration of OT for 10 days in castrated rats compared with untreated castrated rats (Popovic *et al*., 1990). These effects of OT on cellular proliferation have been shown to be due to stimulation of mitotic activity and inhibition of apoptosis of secretory cells in the prostate (Plecas *et al*., 1992). The increase in the weight of the prostate after OT treatment was not accompanied by a rise in plasma gonadotrophins or prolactin (Plecas *et al*., 1992) suggesting that the changes reflected a direct effect of OT on the prostate.

However, there was no change noted in either the prostatic weight or body weight after prolonged administration of OT to intact rats for 28 days (Nicholson and Jenkin, 1995). Although prolonged administration of OT significantly elevated the prostatic T levels throughout treatment, the prostatic DHT levels and 5α-reductase activity increased only after 3 days. This rise in both DHT and 5α-reductase activity was transient and returned to normal within 7 days of treatment. The change in the hormonal milieu with prolonged administration of OT without an accompanied rise in prostatic weight is opposite to its effects on the rat prostate after castration. This suggests that OT interacts with androgens to play a regulatory role in prostatic growth in the intact healthy adult rat.

Daily administration of T to adult rats has been shown to increase the weight of the ventral prostate and decrease the total amount of OT in the prostate. Treatment with the 5α-reductase inhibitor, Finasteride, increased the plasma levels of T and prostatic OT and decreased the DHT levels (Jenkin and Nicholson, 1999).

These studies prompted Nicholson and Jenkin (1995) to suggest a feedback mechanism whereby OT regulates the DHT levels in the rat prostate. In the intact rat, OT stimulates conversion of T to DHT by increasing 5α-reductase activity. The rise in DHT then feeds back negatively to decrease further OT production, and this returns the DHT levels to its normal baseline level.

Development of prostatic hyperplasia is an almost universal feature of the ageing man and dog, and in both species, the process develops only in animals with intact testes. Accumulation of DHT within the prostate, due to either decreased catabolism or increased intra-cellular binding, has been postulated as the hormonal mediator for prostatic hyperplasia in both species, and the process is accelerated by estrogen (Wilson, 1982). Prostatic OT concentrations are significantly higher in old dogs with BPH than in young dogs. This age-dependent increase in prostatic OT concentration is accompanied by an increase in the endogenous 5α-reductase activity (Nicholson and Jenkin, 1995). This is unlike that seen in the intact rat prostate where the increase in prostatic DHT and 5α-reductase activity is transient.

Both hyperplasic and normal epithelial and stromal cells from the human prostate have been shown to stain positively for OT, hNp1 and OTRs (Whittington *et al*., 2004), suggesting a role for this peptide within the human prostate and the development of hyperplasia. Primary culture of prostate tissue from patients with BPH has shown that androgens (T and DHT) and estrogens significantly increase the levels of prostatic OT with a larger effect seen with estrogens (Assinder and Nicholson, 2004). In the ageing male, the levels of DHT decrease but those of T and estradiol remain the same (Shibata *et al*., 2000). This increases the estrogen : DHT ratio and shows a positive correlation with the amount of tissue overgrowth in BPH (Shibata *et al*., 2000) and led Nicholson (1996) to propose an involvement for estrogen in the feedback mechanism of OT in prostate growth.

The development of prostate disorders such as BPH and adenocarcinoma does not occur spontaneously in the ageing rat which is in direct contrast to the situation in humans. Can this be explained by differences or disturbances in the growth regulatory mechanism involving gonadal steroids and OT? In the dog and man are these regulatory mechanisms absent or is the mechanism disturbed in some way thereby leading to the development of growth disorders?

OT has been found to act as a growth regulator through the activation of specific transmembrane G-protein coupled receptors (Cassoni *et al*., 2001). The effects of OT on cellular growth are both tissue and species specific—stimulatory in some tissues and inhibitory in others. These variable effects of OT may be due to linkage of the OTR to different signal induction pathways. In growth-inhibited cells, the effects of OT have been observed to be mediated by the non-conventional cAMP-protein kinase A pathway whilst in growth-stimulated cells, the effects were seen to be mediated by the 'classical' increase in intra-cellular calcium and tyrosine phosphorylation (Cassoni *et al*., 2001).

Differences in the membrane localization of OTRs have recently been seen to have an effect on tissue proliferation (Guzzi *et al*., 2001). It has been shown that OT inhibits cell proliferation when the vast majority of OTRs are excluded from caveolin-1-enriched microdomains (Rimoldi *et al*., 2003). On the other hand, OT has mitogenic effects when the OTRs are targeted to caveolin-1-enriched domains (Rimoldi *et al*., 2003). This indicates that OT can initiate different signalling pathways depending on OTR localization which can then result in either inhibition or stimulation of growth. The epidermal growth factor (EGF) and its receptor [epidermal growth factor receptor (EGFR)] have been localized and synthesized by the rodent and human prostate and are found in prostatic and seminal fluids (Davies and Eaton, 1991). EGFRs have also been localized in normal and abnormal dog prostate cell lines, human BPH tissue and human prostatic carcinoma tissues (Davies and Eaton, 1991). Depending on their localization, OTRs have been shown to transactivate EGFR and activate ERK1/2 by using different signalling intermediates (Rimoldi *et al*., 2003). When OTRs are located outside caveolar

microdomains, the temporal pattern of EGFR and ERK1/2 phosphorylation is different from and is more sustained than when the OTRs are located in caveolar microdomains. Sustained EGFR activation by OTRs located outside the caveolar microdomains has been shown to inhibit cell growth, whereas cell growth is stimulated when the OTRs are located in the caveolar microdomains, and the activation of EGFRs is transient (Rimoldi *et al*., 2003). The anti-proliferative OTR effects achieved by a sustained activation of EGFR and mitogen-activated protein kinase (MAPK) have been postulated to be due to the induction of the cell cycle inhibitor p21 (Rimoldi *et al*., 2003). If this is so, the anti-proliferative effect of OTR should be inhibited by the downstream inhibition of p21. This raises an important question, is BPH a result of stimulation of cellular growth or is it a loss of inhibitory mechanisms?

Clinical applications for OT in male reproductive pathology

The discussed role for locally synthesized OT in male reproductive physiology raises the issue of how this knowledge can be exploited for clinical gain (summarized in Table II).

OT and treatment for male infertility

ICSI is currently the only treatment available to overcome male infertility due to severe irreversible oligo or azoospermia (Kamischke and Nieschlag, 1999). In men with azoospermia not related to hypogonadotrophic hypogonadism, surgical sperm retrieval either from the epididymis or directly from the testis has to be undertaken before ICSI.

OT has been shown, *in vitro*, to improve spermiation and sperm transport in a number of animal models and may therefore improve the quantity of sperm present in an ejaculate. I.v. injection of 50 IU of OT increased the number of spermatozoa in the first ejaculates of electroejaculated Holstein bulls without altering the daily sperm production or the semen quality. This effect of OT was suggested to be potentially advantageous in frozen semen programmes so that less frequent electroejaculation is needed or even a single electroejaculation can be planned (Berndtson and Igboeli, 1988). These animal studies suggest that men with oligospermia may benefit from OT administration.

In a preliminary study, i.v. injection of 0.5 IU of OT to 14 severely oligospermic or azoospermic males given before a second ejaculation improved emptying of spermatozoal stores and reduced the necessity of testicular sperm extraction (TESE) (Rolf *et al*., 2000). A small study on five oligospermic males showed that i.v. bolus injection of 2.5 units OT, 5–10 min before sperm collection by masturbation, almost doubled the number of motile sperm retrieved compared with placebo, without any increase in the ejaculate volume (Filippi *et al*., 2002b). This may have been due to the exogenously administered OT stimulating epididymal contractility and causing a release of the epididymal-stored sperm without having any effect on the accessory sex glands.

In contrast to this, an earlier study administered 16 IU OT intranasally to 49 healthy semen donors before masturbation but did not observe any effect on either the ejaculation time or the semen parameters (Walch, 2001). The half-life of exogenously administered OT is 8–10 min (De Groot *et al*., 1995), and hence optimal plasma concentration of OT may not have been achieved if OT was inhaled too soon before ejaculation. The bioavailability of OT with intranasal application is likely to be variable due to more unpredictable absorption compared to the intravenous route, which may be why even a large dose of 16 IU failed to show any effect. A more recent study (Byrne *et al*., 2003) in 49 men with severe oligospermia used 0.75 IU of OT intravenously <5 min before masturbation. This study also failed to show any effects of OT on ejaculate volume, total sperm count or sperm motility. Although the dose of OT used is larger compared to that used by Rolf *et al*. (2000), it is far less than that used by Filippi *et al*. (2002b). Pharmacokinetic studies in human male volunteers showed that i.v. administration of 1 IU of OT raised plasma OT levels markedly above baseline (De Groot *et al*., 1995). A dose as small as 0.75 IU may not be sufficient to cross the threshold and alter semen parameters in first ejaculates especially in men with intact ejaculatory function.

Many of the studies published so far relating to role of OT in improving sperm output have been fraught with small sample sizes, variable doses and routes of OT administration. Although the more robust study performed by Byrne *et al*. in 2003 had a negative outcome, there remains a need for a large randomized control trial to evaluate the effects of OT in men with severe oligo or azoospermia. Choice of route and dose of OT should take into consideration, the half-life of OT as well as the rates of absorption and bioavailability of OT.

OT and treatment for sexual dysfunction

What is also interesting is the fact that unlike VP, there are no specifically OT-associated pathologies seen due to excessive amounts of plasma OT. Is this due to OT-related abnormalities being lethal and hence never present, or are they so subtle and generalized that they are treated symptomatically? OT is one of the most potent agents known to induce penile erection (Argiolas, 1992). In both men and women, plasma OT levels have been noted to increase during sexual arousal and were significantly higher during orgasm/ejaculation than baseline levels before self-stimulation (Carmichael *et al*., 1987). The presence of OTRs within the penis and the role of OT in penile erection suggest that problems of impotence or with ejaculation may have an underlying OT-related

Table II. Possible clinical applications for oxytocin

Function of oxytocin	Proposed clinical application
Increases spermiation and sperm transport	OT administration to men with oligospermia
Induction of penile erection	Treatment of impotence and ejaculatory disorders
Regulation of cell proliferation	Treatment of benign prostatic hyperplasia
Loss of oxytocin immunoreactivity with the progression of prostatic malignancy	Marker for prostate cancer

defect which as yet has not been recognized, and research into these areas is currently needed.

OT and benign prostatic hyperplasia

BPH is the commonest benign tumour seen in ageing men and affects more than 50% of men over the age of 60 (Berry *et al*., 1984) with the incidence increasing further with age. The physical enlargement of the gland obstructs bladder outflow, and the increase in the resting tone causes a dynamic obstruction to urinary flow (Caine *et al*., 1975). In the prostate, OT affects basal prostatic tone and produces an effect greater than adrenergic agonists in inducing prostatic contractility (Caine *et al*., 1975), suggesting that treatment with OTAs may help to overcome the urinary problems in men with BPH.

In vitro studies confirm that OT, NpI and OTR are present in the hyperplastic prostate (Whittington *et al*., 2004). The suggested indirect role of OT on 5α-reductase activity together with any direct actions OT has on cell proliferation will contribute to excessive cell growth.

The use of OTAs, either alone or in combination therapy with anti-androgens may be helpful for patients with BPH for urinary symptom control and disease progression. Due to actions of OT on tissues elsewhere in the body localized delivery of specific OTAs may be more effective and have fewer side effects. As yet, there have been no studies reported in human male volunteers with BPH, and more research is needed in this field. There is a possibility that in men with BPH treatment with OTAs alone may be unhelpful as it is possible that OT is just one of a list of paracrine factors that work together to stimulate cell growth and proliferation and thus a combination with other treatments may be necessary.

OT and prostatic carcinoma markers

Normal epithelial and stromal cells from the human prostate have been shown to stain positively for OT, hNp1 and OTRs (Whittington *et al*., 2004), suggesting a role for this peptide within the human prostate that may mirror that previously shown in animal studies. Interestingly, OT immunoreactivity appears to be lost with the development of malignant disease (Whittington *et al*., 2004) indicating a role for this paracrine factor in disease progression. OT expression is thus reduced with tumour progression and may provide a marker for invasive disease.

Summary

In conclusion, the traditional image of OT as a purely neurohypophysial hormone with endocrine actions in parturition and lactation has certainly been challenged over the last decade. OT has been shown to be locally synthesized in many organs in both males and females. In the male reproductive tract, OT has been conclusively shown to be a paracrine hormone involved in reproductive tract contractility, steroidogenesis and growth. Although research is ongoing regarding development of new and specific OTAs as tocolytics for the prevention of premature labour, OT and OTAs may also have a role in the treatment of pathologies relating to male reproduction, specifically improving sperm parameters and in the treatment of prostate disorders. A few tentative clinical trials have been conducted to evaluate such claims but, although promising, they have yet to provide conclusive proof. Larger clinical trials and further research are needed to evaluate the use of OT and its antagonists in male reproductive pathology.

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