Oxytocin: a paracrine regulator of prostatic function

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It is now well established that the peptide oxytocin can act as a paracrine factor as well as a classic hormone. Oxytocin is produced locally in both the testis and ovary, where it may modulate both steroidogenesis and contractility of the male and female reproductive tracts. The peptide is also present in the prostate and seminal fluid and there is growing evidence that oxytocin may be produced in the prostate. Within the prostate, oxytocin has been shown to increase growth of the epithelial tissue and increase both muscular tone and contractile activity. Furthermore, prostatic concentrations of the peptide are regulated by androgens. It is hypothesized that oxytocin may act as a paracrine factor to regulate cell growth and that this may be secondary to its effects on the enzyme 5α-reductase which converts testosterone to dihydrotestosterone. In addition, oxytocin may be involved in the pathophysiology of benign prostatic hyperplasia.

The prostate is an enigmatic organ better known, at least in man, for its pathological conditions than for its physiological functions. The prostate contributes a significant proportion of the seminal fluid volume and this fluid contains a variety of substances such as citric acid, fructose, prostaglandins, spermine and zinc, but its precise role remains obscure. Indeed, evidence suggests that the gland is not essential for life and, although involved in, is not essential for reproduction.

The prostate lies at the base of the bladder and consists of many acini lined with secretory epithelial cells which drain, via a series of ducts, into the urethra. This glandular tissue is surrounded by stromal tissue containing smooth muscle fibres. In rats, the prostate is organized into three distinct lobes, but in both men and dogs, these are not apparent and exist only as zones in what appears to be a single uniform gland (Cunha et al., 1987).

Disease of the prostate is common in men and dogs and relates to abnormalities of growth of the gland, both hyperplastic and neoplastic. Growth of the prostate is regulated by androgens and within the prostate testosterone is converted to the active androgen, dihydrotestosterone (DHT), by the enzyme 5α-reductase. Dihydrotestosterone acts via the androgen receptor to stimulate both growth and secretion of prostatic fluid. This promotion of growth is not a direct androgen effect but is probably mediated by growth factors such as epidermal growth factor (see Steiner, 1993). Furthermore, oestrogens can act synergistically with androgens to regulate prostatic growth.

Oxytocin

Oxytocin is a nonapeptide secreted by the hypothalamo-neurohypophysial system with well documented roles in parturition and lactation. More recently, it has been shown to be produced locally in a variety of tissues including the female and male reproductive tracts (Wathes, 1989). In males, oxytocin is produced by the testicular Leydig cells (Nicholson and Hardy, 1992) and is regulated by the gonadotrophin LH and factors from the seminiferous epithelium (Nicholson et al., 1994). Two possible roles for the peptide have been demonstrated: first, as a regulator of seminiferous tubule contractility and thus sperm transport and second, as a modulator of steroidogenesis.

An oxytocin-like peptide has also been identified in the mammalian prostate and in seminal fluid (Nicholson and Jenkin, in press). This peptide has similar chromatographic properties to the hypothalamic hormone, and prostatic concentrations are an order of magnitude higher than those found in the plasma (Nicholson and Jenkin, in press). Although the origin of prostatic oxytocin is not established, the evidence that concentrations of the peptide are not reduced by orchidectomy or epididymo–orchidectomy rules out a testicular source of the peptide. Furthermore, the identification of mRNA encoding oxytocin in the human prostate and the fact that prostatic concentrations are higher than plasma concentrations support the idea of local synthesis (Nicholson and Jenkin, in press). What role, if any, does oxytocin have in the prostate? Is it involved with the regulation of steroid production and contractility as in the testis, or is it just another constituent of seminal fluid?

Effects of oxytocin on growth

There are relatively few published investigations on the effects of oxytocin in the prostate. However, some early workers observed that administration of oxytocin increased the size of accessory sex glands in testosterone-supplemented, castrated rats (Debackere et al., 1961) and also increased the height of epithelial cells in the rabbit prostate (Armstrong and Hansel, 1958). Popovic et al. (1982) demonstrated that oxytocin can increase the growth of the ventral prostate in castrated rats. However, effects were seen only in intact rats if the animals also had low circulating concentrations of gonadotrophins and prostate weight (Hristic et al., 1985). Oxytocin administration for 10 days after castration significantly increased prostate weight and was associated with an increased epithelial volume.
and the presence of larger acini (Popovic et al., 1990). These changes have been shown to be due to both a stimulation of mitotic activity and a decrease in apoptosis in the epithelial cells (Plecas et al., 1992) and may also reflect an increased secretion of prostatic fluid.

The mechanism of these growth effects is unknown. The peptide may have a direct mitogenic effect, since oxytocin has been demonstrated to stimulate mitosis in liver and adrenal cells in vitro (Payet and Isher, 1976). However, no mitogenic effect was seen when epithelial cells from the rat ventral prostate were incubated with oxytocin (McKeehan et al., 1984). Alternatively, oxytocin may act indirectly by modulating local concentrations of androgens. In the testis, oxytocin can regulate steroidogenesis in two ways: first, by altering production of testosterone itself (Adashi and Hsueh, 1981) and second, by increasing the conversion of testosterone to its 5α-reduced metabolites (Nicholson and Jenkin, 1994).

Administration of oxytocin to adult rats either subcutaneously or via intratesticular implants is accompanied by a persistent increase in plasma and testicular concentrations of DHT and increased activity of the enzyme 5α-reductase (Nicholson et al., 1991; Nicholson and Jenkin, 1994). More recent work has shown that, while prolonged treatment with oxytocin results in a sustained increase of 5α-reductase activity in the testis and epididymis, this is not the case in the prostate. Here, 5α-reductase activity and prostatic DHT concentrations are raised after 3 days of oxytocin treatment, but both factors have returned to control values after oxytocin administration for 7 days. These findings may explain why no change in morphology of the prostate is seen when oxytocin is given to intact adult rats for 7 days (Popovic et al., 1990). Thus, in healthy adult rats, it appears that oxytocin produces only a transient increase in DHT concentrations, and presumably, prostatic growth. This may represent a homeostatic mechanism, since continued growth of the prostate is neither required nor desirable once sexual maturity is reached.

If oxytocin is involved in this regulatory mechanism it, too, should be affected by other prostatic factors such as androgens. As mentioned earlier, reduction of circulating androgens by castration, although leading to a decrease in prostate weight, results in increased concentrations of prostatic oxytocin (Nicholson and Jenkin, in press). Furthermore, when testosterone propionate is given to either castrated or intact rats, both total prostatic oxytocin and the concentration of the peptide are significantly reduced, whereas administration of the antiandrogen, cyproterone acetate, increases prostatic oxytocin concentration (Nicholson and Jenkin, in press). Thus, it appears that prostatic oxytocin is negatively regulated by androgens, but whether the androgen involved is testosterone or DHT is as yet unclear. Oestrogens may also be involved, since they act synergistically with testosterone to promote prostatic growth and in the female can increase plasma oxytocin concentrations. Thus, one can hypothesize that in healthy rats, oxytocin increases conversion of testosterone to DHT, which then feeds back to inhibit further oxytocin production and thus returns DHT to basal concentrations (Fig. 1). This mechanism may also involve changes in oxytocin receptor concentrations within the prostate. Oxytocin receptors have been demonstrated in the testis, epididymis and seminal vesicles (Maggi et al., 1987; Bathgate and Sernia, 1994) but have not yet been identified in the prostate.

These data provide some evidence for a physiological function for oxytocin, but does the peptide play a role in the pathology of the gland? Benign prostatic hyperplasia (BPH) is the commonest benign tumour seen in men and affects more than 50% of men over the age of 60 (Berry et al., 1984). It results in both a physical enlargement of the gland, which is initially mainly in the periurethral area, which may obstruct the bladder outflow, and an increase in muscular tone, which contributes a dynamic component to the physical obstruction (Caine et al., 1975). Benign prostatic hyperplasia affects dogs as well as
men and, although the aetiology of the disease is complex, two factors – ageing and androgens – are known to be involved in the development of this disease.

Using the dog as a model, we have begun to investigate whether oxytocin concentrations change in animals with BPH. Prostatic oxytocin concentrations are significantly higher in old dogs with BPH than in young dogs. Activity of 5α-reductase is also significantly increased in prostatic tissue from old dogs with histologically proven BPH (Nicholson and Jenkin, in press). As mentioned earlier, increased oxytocin concentrations in rats were accompanied only by a transient rise in enzyme activity; thus it would appear that either dogs do not have a similar feedback mechanism controlling prostatic oxytocin concentrations or perhaps this feedback mechanism is altered during the development of BPH. Prostatic oxytocin concentrations are also higher in men with BPH when compared with tissue from patients with carcinoma of the prostate (Fig. 2), but as normal human tissue is difficult to obtain, it is not known if this represents an increase in the case of BPH or whether concentrations are reduced in the malignant gland.

These data provide circumstantial evidence that oxytocin can stimulate growth of the prostate and that the peptide may play a role in the pathological growth of the gland in BPH. In BPH, the obstruction is not only due to an increase in the size of the gland but also to a dynamic component caused by an increased muscular tone of the gland. Oxytocin is known to stimulate contractile activity in other areas of the reproductive tract. Indeed, the peptide has been shown to increase the contractility of seminiferous tubules, epididymis and ductus deferens (see Wathes, 1989). Within the prostate, both adrenergic and cholinergic systems modulate motor activity. Oxytocin can also both increase the tone of the prostate and stimulate muscular contractions in prostate tissue from a variety of species (Bodanszky et al., 1992) and is more potent than noradrenaline or methacholine. Therefore, oxytocin may be involved in the maintenance of prostatic tone and in the co-ordinated contraction of the gland at ejaculation. Furthermore, the increased concentrations of peptide recorded in tissue from glands with BPH may contribute to the increased muscular tone and dynamic obstruction to the bladder observed in this disease.

In conclusion, there is new evidence that oxytocin is present and may be produced by the mammalian prostate and, within the gland, may play a physiological role in the regulation of growth and muscular contractility. There is also growing evidence to implicate the peptide in the pathophysiology of benign prostatic hypertrophy, where oxytocin may contribute to both the physical enlargement and dynamic tone of the gland. Such a role raises the possibility of using specific oxytocin antagonists either as prophylactic agents, to prevent growth of the prostate, or therapeutically, to reduce the muscular tone of the gland and thus alleviate symptoms.

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Key references are identified by asterisks.


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