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Neuroendocrine peptides in the prostate

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Abstract Circulating androgens are required for normal growth and maintenance of function of the prostate. However, the prostate also contains neuroendocrine peptides, found either in nerve terminals or in prostatic neuroendocrine cells, which are likely to regulate prostate growth or function. The neuronal peptides are likely to participate in the regulation of the synthesis and secretion of prostatic secretory products. While the function of the neuroendocrine cells is undefined, there is evidence for growth-regulating effects of several neuroendocrine cell peptides. Since neuroendocrine differentiation has been correlated with tumor grade and poor prognosis in prostate cancer, the peptide products of the neuroendocrine cells may influence cancer cell replication as well. Recent evidence in other tissues suggests that peptide hormone receptor second-messenger systems may interact with steroid receptors to modulate their actions. These findings raise the possibility that prostatic neuroendocrine peptides may modulate the response of prostate to androgens.

Key words Prostate · Prostate carcinoma · Neuropeptides · Neuroendocrine cells

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Hormonal regulation of the prostate gland is usually described in terms of the effects of circulating androgens. Androgens, particularly dihydrotestosterone, are required for the normal development and maintenance of function of the prostate. The prostate gland also contains a number of neuroendocrine peptides located either within nerve terminals or within prostate neuroendocrine cells, many of which have known biologic activity in other organ systems (Table 1). While the biologic functions of these peptides in prostate physiology have not been fully elucidated, it is likely that they play a role, either by acting as neurotransmitters or as paracrine or autocrine factors. Alterations in expression of these neuroendocrine peptides associated with benign prostatic hypertrophy and with prostate cancer may be important in the pathophysiology of these diseases.

Neuroendocrine anatomy of the prostate

The prostate neuroendocrine system is composed of the autonomic and sensory innervation of the prostate and of neuroendocrine cells present in the epithelial layer of the prostatic acini and ducts. Autonomic innervation of the prostate derives from the pelvic plexus and is composed of sympathetic nerves derived from the hypogastric nerve and parasympathetic nerves derived from pelvic splanchnic nerves [57]. Autonomic, presumably parasympathetic, ganglia are distributed in the capsule and throughout both the peripheral and central human prostate. In general, the greatest density of nerve fibers is found in the central regions of the prostate, with relatively fewer fibers in the peripheral zone where there are also fewer glandular acini. Most nerve fibers are found in the stromal compartment surrounding the prostatic acini, either running parallel to the smooth muscle fibers or following blood vessels. By immunohistology, several neuroendocrine peptides have been identified in these nerve fibers. The greatest number of fibers contain neuropeptide Y or

Table 1 Neuroendocrine peptides in prostate

Autonomic nerves
Neuropeptide Y
Vasoactive intestinal peptide
Met-enkephalin
Leu-enkephalin
Somatostatin
Sensory nerves
Calcitonin gene-related peptide
Substance P
Neuroendocrine cells
TSH-like peptide
Gastrin-releasing peptide (bombesin-like)
Calcitonin
Calcitonin gene-related peptide
Somatostatin
Chorionic gonadotropin
Glucagon
ACTH
Leu-enkephalin
β-Endorphin
Parathyroid hormone-related peptide
Undefined cellular origin
Gonadotropin-releasing hormone
Thyrotropin-releasing hormone
pGlu-Glu-Pro-NH_2
pGlu-Phe-Pro-NH_2

vasoactive intestinal peptide [20, 40]. Other fibers also contain calcitonin gene-related peptide, substance P, met- or leu-enkephalin, or somatostatin immunoreactivity [20]. Although the neuronal distribution of neuroendocrine peptides in the rat prostate has not been studied, rat prostate also contains extensive autonomic innervation [62].

The other component of the prostate neuroendocrine system is neuroendocrine cells. Prostatic neuroendocrine cells were first identified by Pretl a half century ago [51] and have been recently described in both normal and malignant prostate tissue [2, 19, 24]. Prostatic neuroendocrine cells are currently characterized by the presence of immunostaining for various neuroendocrine products, of which the most frequently identified is chromogranin A, a neurosecretory peptide commonly found in neuroendocrine cells of other tissues [3, 4]. Prostatic neuroendocrine cells are scattered throughout the epithelial layer lining the prostatic acini and ducts and are also present in the epithelium of the prostatic urethra. These cells may be present on the basement membrane of the acini or on top of the basal cell layer. Two morphologic types of prostatic neuroendocrine cells are commonly identified. "Open" cells have dendritic processes connecting the neuroendocrine cell with the lumen of the acinus. "Closed" cells may also have dendritic processes extending between adjacent cells, but not connecting with the lumen. Their morphology is similar to that of other epithelial neuroendocrine cells including those of the gut and respiratory tract [2, 4, 19, 23].

The embryologic origin of the prostatic neuroendocrine cells is uncertain, but current evidence suggests that they are not of neural crest origin, but rather derive from the differentiation of prostate epithelial stem cells. This hypothesis is based in part on the finding that both primary and metastatic prostatic adenocarcinomas contain malignant neuroendocrine cells, which implies that neuroendocrine cells in prostate cancers are malignant cells rather than cells that have simply been trapped by the tumor [24]. This finding suggests that prostate cancers may derive from a common stem cell capable of generating either secretory epithelial or neuroendocrine cells. This hypothesis is supported by the recent identification of immunoreactive prostate-specific antigen in some prostate neuroendocrine cells [4]. Since neuroendocrine cells may have a common origin with other prostate epithelial cells, androgen receptors have also been sought in neuroendocrine cells. While two studies have failed to detect androgen receptors [8, 39], one study identified nuclear androgen receptor immunoreactivity in a subset of both normal and malignant neuroendocrine cells [46]. It is currently unknown whether mature neuroendocrine cells are androgen responsive. In an autopsy study of the developmental expression of neuroendocrine cells in humans, neuroendocrine cells were not identified in the prostates of prepubertal subjects except in very young infants, suggesting that normal neuroendocrine differentiation is an androgen-responsive process [19]. However, as discussed below, androgen ablation in adults with prostate cancer is associated with an increased number of malignant neuroendocrine cells, a result that suggests that malignant neuroendocrine cells may not be androgen dependent [3].

While the most frequently identified biologically active product of neuroendocrine cells is serotonin [2, 4], these cells also produce several neuroendocrine peptides. Most commonly identified is a novel peptide that cross-reacts with polyclonal antisera to thyroid-stimulating hormone (TSH) [1, 4]. This peptide is not identical to human TSH since it is not identified by monoclonal antisera to the α-subunit of TSH. SDS-polyacrylamide gel electrophoresis analysis reveals a 32-kDa peptide that is detected by monoclonal antibodies to the carboxyl terminal but not to the midregion of the TSH β-subunit. Therefore, this peptide appears to be distinct from the known 18-kDa TSH β-subunit, but may share some sequence homology at the carboxyl terminus [1]. Calcitonin has been identified by immunocytochemistry and radioimmunoassay in a subset of prostate neuroendocrine cells [1, 24]. Calcitonin has been further colocalized with serotonin into secretory granules in prostatic neuroendocrine cells by immunoelectron microscopy [25]. The parathyroid hormone-related protein, associated with hypercalcemia in some malignancies, has also been identified in prostate cancers [36], and was localized to neuroendocrine cells [37]. In addition to these peptides, immunoreactive calcitonin gene-related peptide, gastrin-releasing peptide, somatostatin, chorionic gonadotropin, adrenocorticotropic hormone, glucagon, β-endorphin, and leu-enkephalin have been identified in some neuroendocrine cells [2, 4, 23–25].

The prostate is also the source of a number of neuroendocrine peptides whose specific cellular localization has not been identified. Both human and rat prostate

contain thyrotropin-releasing hormone (TRH, pGlu-His-Pro-NH_2) as well as at least two TRH-like peptides [48, 49]. pGlu-Glu-Pro-NH_2 was first identified as the major TRH-like peptide in rabbit prostate [16]; it was also demonstrated in human [45] and rat prostate [59] and in rabbit and human semen [15]. The major TRH-like peptide in human and rat prostate is an uncharged peptide [30, 48]. pGlu-Phe-Pro-NH_2 was purified from human semen [38]; we have subsequently identified this predominant uncharged iTRH in both rat and human prostate [31]. The expression of these peptides in the prostate is of some interest, since the prostate also contains a TSH-like peptide that could potentially be regulated by TRH-related peptides. Gonadotropin-releasing hormone (GnRH) immunoreactivity has been identified in biopsy specimens from prostatic carcinomas and from benign enlargement of the prostate [52]. It is not known whether GnRH is a product of normal prostate cells.

Role of neuronal peptides

The importance of prostatic innervation in normal physiology has been traditionally ascribed to the classic autonomic neurotransmitters norepinephrine and acetylcholine. The coordinated effects of sympathetic and parasympathetic nerves are thought to be important in prostate secretion during ejaculation. Cholinergic agents are reported to enhance the rate of secretion by the prostate, while α-adrenergic agonists stimulate smooth muscle contraction and expression of the prostatic contents into the urethra [9, 63]. In addition to these acute effects, autonomic innervation of the prostate may also play a chronic role in the maintenance of normal prostate structure and function. Surgical denervation of the rat ventral prostate produces a significant decrease in prostate weight after 3 weeks. This effect is associated with a decrease in the height and volume of secretory epithelial cells without a decrease in cell number. Ultrastructural changes consistent with a decrease in secretory activity as well as an apparent decrease in accumulation of lumenal secretory materials were also described [64]. These results suggest that autonomic neurotransmitters are important both in the regulation of chronic secretory activity and in the acute production and expression of prostate secretions.

Recent evidence suggests that neuropeptides contained in prostatic autonomic nerves may play a role in the regulation of prostatic function. The best studied of these neuroendocrine peptides is vasoactive intestinal peptide (VIP), which is abundant in autonomic nerves surrounding the prostatic acini in humans [20, 40]. While VIP is typically present in cholinergic nerves in other tissues, this association has not been definitely proven in prostate. Normal rat prostate epithelial cells have been shown to contain VIP receptors and to produce cAMP in response to VIP [11, 12]. Although the effects of VIP on normal human prostate epithelial cells have not been studied, the well-differentiated, androgen-responsive human prostate cancer cell line LNCaP also contains VIP receptors and produces cAMP in response to VIP [34]. β-adrenergic receptors are also present in rat prostate epithelial cells [26], but VIP is a more potent stimulator of adenyl cyclase in epithelial cells than is the β-adrenergic agent isoproterenol [11]. It is therefore possible that VIP plays a role in regulating the secretory function of normal prostate epithelial cells. While VIP does not stimulate mRNA synthesis for prostate-specific antigen in LNCaP cells [34], its role in the synthesis and secretion of prostate-specific antigen or other secretory products by normal epithelial cells has not been extensively investigated.

The most widely distributed neuroendocrine peptide in prostatic autonomic nerves is neuropeptide Y (NPY) [20]. In other tissues in the male reproductive tract NPY is found in sympathetic nerves, where it is localized and coreleased with norepinephrine [60]. However, this association has not been proven in prostate. While the function of NPY in the prostate is currently unknown, studies of the effects of NPY elsewhere in the nervous system have demonstrated a role to inhibit the effects of other neurotransmitters. NPY has been shown to inhibit the release of norepinephrine from sympathetic nerve terminals in the vas deferens of rats and guinea pigs [60]. NPY also acts to inhibit the effects of several neurotransmitters by inhibiting the activation of adenyl cyclase. This effect is mediated by a receptor-coupled inhibitory G protein. In particular, NPY has been shown to inhibit cAMP production stimulated by α- or β-adrenergic agonists or by VIP in several cell types, including rabbit colonic mucosal cells, bovine adrenal chromaffin cells, and rat pinealocytes [5, 33, 69]. These findings suggest that NPY in the prostate could act either to modulate sympathetic stimulation of prostate contraction or to modulate the effects of VIP or other neurotransmitters on prostate epithelial cells. In a recent study of the effects of neuroendocrine peptides on smooth muscle contraction in the rat urogenital tract, NPY did not produce contraction of prostatic smooth muscle, nor did it inhibit phenylephrine-induced contraction of prostate muscle [65]. The effects of NPY on prostate secretion have not been extensively studied.

Among the other peptides present in prostatic nerves, calcitonin gene-related peptide (CGRP) and substance P are traditionally associated with sensory fibers and pain sensation. In the prostate, CGRP relaxes phenylephrine-induced contraction of smooth muscle, suggesting a modulating role in prostate contractile responses [65]. A role for CGRP in regulating the function of secretory epithelial cells has not been described. However, we have recently demonstrated that CGRP stimulates cAMP accumulation in several cultured human prostate cancer cell lines [30], which indicates a possible function for CGRP in epithelial cells. The actions of enkephalins and somatostatin remain to be elucidated.

Role of neuroendocrine cell peptides

The role of the neuroendocrine cells in normal prostate function is less well defined than that of the autonomic

nerves. However, the location and structure of these cells suggest at least two possible physiologic actions. Prostate neuroendocrine cells are located within the prostate epithelium, adjacent to secretory epithelial cells. Dendritic processes of the neuroendocrine cells often extend between adjacent epithelial cells, which raises the possibility that neuroendocrine cell peptide products act as paracrine factors to regulate the growth or function of adjacent epithelial cells [2, 23]. In this hypothesis, the dendritic processes could either serve as secretory structures or as sensory structures that receive signals from the adjacent cells or lumen to regulate the paracrine secretory activity of the neuroendocrine cell. In a recent study of the relationship between neuroendocrine differentiation and cell proliferation in human prostate, epithelial cells that were immunoreactive for the proliferation-associated antigen Ki-67 tended to be located in close proximity to neuroendocrine cells in both normal and malignant prostate tissue. The neuroendocrine cells themselves did not express Ki-67, which suggests that they were terminally differentiated and not dividing [7]. This study supports a relationship between neuroendocrine cells and epithelial proliferation and suggests the possibility that neuroendocrine peptides play a role in prostate cell replication.

The existence of a dendritic process connecting the neuroendocrine cells to the acinar lumen also suggests that neuropeptides may be secreted into the prostatic fluid and play a role in fertility. Several neuroendocrine peptides have been identified in semen and are likely to be products of the prostatic neuroendocrine cells. These peptides include TRH, pGlu-Glu-Pro-NH_2, pGlu-Phe-Pro-NH_2, calcitonin, somatostatin, β-endorphin, met-enkephalin, and bombesin-like immunoreactivity [15, 28, 32, 38, 49, 54]. TRH and pGlu-Glu-Pro-NH_2 have been found to increase sperm motility [59], while calcitonin inhibits sperm motility in vitro [28].

Benign prostatic hypertrophy

The role of α-adrenergic innervation of the prostate in the pathogenesis of urinary obstruction secondary to benign prostatic hyperplasia (BPH) has formed the basis for the use of α-adrenergic blockers in the therapy of this disease [41]. Less is understood about the role of neuroendocrine peptides in this disorder. Changes in both the innervation of prostate and the expression of neuroendocrine cells have been noted in BPH. In a study of urinary obstruction in patients with BPH, an overall decrease in immunostaining for fibers containing neuroendocrine peptides was found in most regions of the prostate in patients with obstruction compared to unobstructed patients. However, the number of VIP- and CGRP-immunoreactive fibers was increased in the peripheral zones of prostates from patients with urinary obstruction [13]. Since the functions of these peptides in normal prostate are not fully elucidated, the physiologic importance of these findings is unknown.

Neuroendocrine cells are also present in prostates of humans with BPH. The numbers of neuroendocrine cells have been reported either to be decreased or increased in BPH [2]. In part, this variance may reflect regional differences in expression of neuroendocrine cells. Since neuroendocrine cells are not part of the stromal compartment, they are relatively less frequent in BPH, where stromal hyperplasia predominates. However, it was recently shown that while the overall number of neuroendocrine cells is decreased in BPH, focal areas of increased neuroendocrine differentiation are noted in small, presumably immature, BPH nodules [14]. This finding was interpreted to suggest that the presence of neuroendocrine cells may mark growth foci in BPH.

The qualitative expression of neuroendocrine peptides does not differ between normal and BPH tissue, in that the same neuroendocrine peptides are identified in both BPH and in normal tissue [2]. However, on a tissue-weight basis, immunoreactive calcitonin [21] and serotonin [14] levels were found to be substantially lower in BPH than in normal prostate. This finding may again reflect the prominence of the stromal compartment in BPH.

Prostate cancer

Considerable recent interest has focused on the role of neuroendocrine cells and their peptide products in prostate cancer. Neuroendocrine cells are reported in recent studies to be present in 50–100% of prostate cancers [4, 17, 18, 23, 24, 61]. The numbers of neuroendocrine cells range from a few scattered cells to larger numbers of cells occasionally occurring in clusters. Rare prostate tumors with small cell or carcinoid histology are composed entirely of neuroendocrine cells [23]. The variability of neuroendocrine cell number has led to the concept that prostate cancers exhibit varying degrees of neuroendocrine differentiation. Several studies have examined the association of neuroendocrine differentiation with tumor histology and clinical outcome. Cohen et al. [18] studied 90 patients with prostate cancer whose initial biopsies were graded for the presence or absence of neuroendocrine differentiation. Of the 46 patients who died of metastatic prostate cancer during the 4- to 9-year follow-up period, 42 patients had neuroendocrine cell-positive tumors on initial biopsy. Of the 44 survivors, only 5 had neuroendocrine cell-positive tumors. Abrahamsson et al. [3] analyzed serial prostate biopsies from 25 patients with low-grade prostate cancer (stages A1, A2, or B1), treated with estrogen therapy. Over 3–11 years of follow-up, a worsening of tumor histology was observed that generally correlated with an increase in neuroendocrine differentiation. These results suggest that neuroendocrine differentiation is a marker of poor prognosis in prostate cancer and may correlate with development of the androgen-resistant state. In contrast to these findings, Aprikian et al. [4] recently reported a cross-sectional histopathologic study of prostates from 31 patients with

untreated prostate cancer and 21 patients treated for 3 months with diethylstilbestrol before prostatectomy. In this study no relationship was identified between neuroendocrine differentiation and either Gleason score or pathologic stage. No difference in neuroendocrine differentiation was appreciated between prostates from untreated and from estrogen-treated patients. However, the duration of estrogen treatment was much shorter in this study than in that of Abrahamsson et al. It has also been suggested that neuroendocrine cells belong to a subset of prostate carcinoma cells that are androgen independent, and that their presence therefore reflects the extent of overall differentiation of the tumor into a less well differentiated, androgen-independent phenotype. This concept is supported by the fact that small-cell and carcinoid prostate cancers are resistant to treatment by androgen ablation [58]. Two studies have reported that prostate neuroendocrine cells do not contain androgen receptors [8, 39], while another study identified androgen receptor immunoreactivity in a subset of neuroendocrine cells [46]. The presence of functional androgen receptors in prostate neuroendocrine cells has not yet been demonstrated. It therefore remains uncertain whether prostate neuroendocrine cells are androgen responsive.

Additional interest in prostate neuroendocrine cells relates to the possibility that neuroendocrine peptide products of these cells may influence the behavior of the tumors. The recent evidence, discussed above, that neuroendocrine cells tend to occur in close proximity to proliferating cells in prostate adenocarcinomas suggests the possibility that neuroendocrine peptides may stimulate the growth of prostate adenocarcinoma cells [7].

Among the best-described neuroendocrine peptide growth factors are members of the bombesin family. Bombesin is an amphibian peptide whose human homologs include gastrin-releasing peptide (GRP) and neuromedins B and C. Bombesin and GRP stimulate growth in numerous cell types, including Swiss 3T3 cells, bronchial epithelial cells, and human small cell lung cancer [53, 66, 67]. A subset of both normal and malignant prostate neuroendocrine cells contains immunoreactive GRP [4, 22]. Recent studies have also demonstrated a growth-proliferative effect of bombesin on prostate cancer cells in vitro, suggesting that GRP in prostate cancers may have a similar effect [6]. Bombesin has also been shown to increase the ability of LNCaP and PC-3 prostate cancer cells to invade the reconstituted basement membrane Matrigel [34]. Thus, GRP may stimulate both the growth and invasiveness of prostate cancer cells.

Gonadotropin-releasing hormone (GnRH) analogs have been used in the treatment of prostate cancer because of their actions to decrease pituitary gonadotropin secretion, thereby reducing serum testosterone levels [55]. However, recent studies have suggested that GnRH may also directly affect the growth of prostate cancers. Although GnRH has not yet been identified in normal prostate, GnRH has been identified in prostate cancer tissue and in specimens from BPH. GnRH-like immunoreactivity (its identity to authentic GnRH confirmed by high-performance liquid chromatography) has also been identified in LNCaP and DU-145 human prostate cancer cell lines. In the same study, GnRH immunoreactivity was identified in the majority of prostate cancer samples examined, but in less than half of the benign tumors. In addition, high-affinity binding sites for GnRH have also been found on both benign and malignant prostate cells [52]. GnRH agonists were shown to have dose-dependent effects to inhibit the growth of LNCaP cells [42]. Conversely, treatment of GnRH-producing LNCaP cells with GnRH antagonists stimulated their growth [43]. These effects appeared to be mediated by an effect of GnRH to inhibit DNA synthesis without inhibiting protein synthesis [42]. These results suggest that GnRH agonists may inhibit the growth of prostate cancers by direct effects on cell division as well as indirect effects mediated through lowering serum testosterone levels. GnRH itself may have autoregulatory effects to inhibit prostate cancer growth.

Calcitonin is frequently found in neuroendocrine cells in prostate cancer. While calcitonin-immunoreactive cells typically represent a subset of neuroendocrine cells in the tumor, some prostate cancers with extensive neuroendocrine differentiation have been reported to contain large numbers of calcitonin-containing neuroendocrine cells. Some of these tumors were shown to secrete calcitonin into the circulation [27]. Prostate cancer cells in culture have been found to secrete calcitonin into the medium [56]. The physiologic effect of calcitonin in prostate cancer is unknown. However, we have recently identified calcitonin receptors in the human prostate cancer cell line DU-145 [29].

Although less extensively studied, other peptides have been shown to have effects on prostate cancer behavior. VIP was shown to stimulate the invasive potential of LNCaP cells but not PC-3 cells by a mechanism associated with the generation of cAMP [34]. Parathyroid hormone-related peptide (PTHrP) immunoreactivity has been identified in human prostate cancer tissues [36]. PTHrP production is associated with hypercalcemia in a number of other malignancies. Although uncommon, hypercalcemia does occur with some prostate cancers [44] and may potentially also be associated with PTHrP production. PTHrP has also been reported to act as an autocrine growth factor in some tumors [10] and is potentially involved in regulating prostate cancer cell growth. Expression of TRH and the TRH-like peptides pGlu-Glu-Pro-NH_2 and pGlu-Phe-Pro-NH_2 is reduced in prostate cancers when compared to BPH tissue [30].

Interaction of neuroendocrine peptides with androgens

While steroid hormones and peptide hormones are commonly thought to act via independent pathways, a number of recent studies have suggested that peptide hormone signaling pathways may modify the cellular response to steroid hormones. Peptide hormones produce their effects by binding a cell surface receptor and activating second-messenger pathways that result in the activation of protein kinases. These activated protein kinases

phosphorylate other proteins, leading ultimately to the generation of a cellular response. Steroid hormones produce effects on gene transcription by binding to a receptor, which then interacts with a regulatory region on the steroid-regulated gene. Phosphorylation of transcription factors, including hormone receptors, is often an important event in the activation of gene transcription [47]. A number of recent studies have shown that activation of protein kinases by typical peptide hormone second messengers such as cyclic AMP can modify the response of a steroid hormone receptor to its ligand. In fact, certain steroid hormone receptors can be activated by alternate second-messenger pathways in the absence of the steroid ligand [35, 50, 68]. Although steroid-peptide hormone interactions have not been investigated in the prostate, these results obtained in other steroid hormone-responsive tissues suggest the possibility that the androgen and neuroendocrine peptide hormonal systems in the prostate may interact in the regulation of prostate growth and function.

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