Organogenesis 9:3, 206–215; July/August/September 2013; © 2013 Landes Bioscience

Age-related changes in the innervation of the prostate gland

Implications for prostate cancer initiation and progression

Carl W White, Jin Han Xie and Sabatino Ventura*

Drug Discovery Biology; Monash Institute of Pharmaceutical Sciences; Monash University; Parkville, VIC Australia

Keywords: autonomic nervous system, acetylcholine, adrenoceptors, muscarinic receptors, noradrenaline, parasympathetic nervous system, sympathetic nervous system

Abbreviations: ATP, adenosine 5'-triphosphate; BPH, benign prostatic hyperplasia; cAMP, cyclic adenosine monophosphate; CGRP, calcitonin gene-related peptide; DHT, dihydrotestosterone; LUTS, lower urinary tract symptoms; PDE, phosphodiesterase; PSA, prostate specific antigen; TGFβ, transforming growth factor β; VIP, vasoactive intestinal polypeptide

The adult prostate gland grows and develops under hormonal control while its physiological functions are controlled by the autonomic nervous system. The prostate gland receives sympathetic input via the hypogastric nerve and parasympathetic input via the pelvic nerve. In addition, the hypogastric and pelvic nerves also provide sensory inputs to the gland. This review provides a summary of the innervation of the adult prostate gland and describes the changes which occur with age and disease. Growth and development of the prostate gland is age dependent as is the occurrence of both benign prostate disease and prostate cancer. In parallel, the activity and influence of both the sympathetic and parasympathetic nervous system changes with age. The influence of the sympathetic nervous system on benign prostatic hyperplasia is well documented and this review considers the possibility of a link between changes in autonomic innervation and prostate cancer progression.

The adult prostate gland grows and develops in an age-dependent manner. In aged males this development gives rise to abnormalities which are benign [benign prostatic hyperplasia (BPH)] and/or malignant (prostate cancer). Seemingly in parallel, autonomic nervous system activity changes in men with age, and this has been associated with diseases such as hypertension and BPH. This review describes the innervation of the prostate gland through the stages of adult life and explores the possibility that changes in autonomic nervous system activity may contribute to prostate cancer initiation and/or progression.

Fetal and Prepubescent Prostate Development

Morphogenesis of the human prostate gland occurs around the tenth week of gestation when circulating fetal androgen levels stimulate the differentiation of the endodermal urogenital sinus, causing the formation of solid epithelial outgrowths (prostatic buds).[1] The prostatic buds rapidly lengthen, arborize, cannulate and cytodifferentiate into basal and luminal epithelium.[1] The newly formed tubuloalveolar ducts grow and spread throughout the urogenital mesenchyme, which concurrently differentiates and matures into the smooth muscle-containing prostatic stroma. The growth and maturation of the tubuloalveolar ducts and stroma is dependant on androgens as well as the interaction between the urogenital mesenchyme and epithelial growths.[1] By the thirteenth week of gestation, there are approximately 70 primary ducts surrounding the developing urethra and by birth ductal branching is complete.[1] The pre-pubertal prostate is small, weighing approximately 2 g, and due to the low levels of testosterone, growth of the prostate during this period is limited.[2]

Prior to puberty, the prostate gland is quiescent and presumably not influenced by the autonomic nervous system. At the beginning of puberty, secretion of androgens from the testes cause the prostate to undergo a period of rapid development and growth ultimately reaching its full size and mature morphology by 18–20 y.[2]

The Young Adult Prostate Gland

The young adult prostate weighs approximately 20 g and is the largest of the male accessory reproductive organs. It is an alobular structure found posterior to the bladder that completely encapsulates the prostatic urethra and ejaculatory ducts.[2] The glandular elements of the prostate are made up of branching tubuloalveolar ducts with numerous secretory acini, surrounded by a thin fibromuscular stroma. The glandular elements or zones, which produce and drain prostatic secretions into the urethra, account for approximately 70% of the total prostate bulk with the fibromuscular stroma, comprising of connective tissue and smooth muscle, making up the remaining 30%.[3]

While testosterone is the primary circulating androgen produced by the testes, in peripheral tissues such as the prostate,

*Correspondence to: Sabatino Ventura; Email: Sab.Ventura@monash.edu
Submitted: 03/18/13; Revised: 04/23/13; Accepted: 04/26/13
http://dx.doi.org/10.4161/org.24843

testosterone is converted locally to dihydrotestosterone (DHT) by the action of the enzyme 5α-reductase.[4] DHT is more potent than testosterone and has a higher affinity for the nuclear androgen receptor.[5] Activation of the androgen receptor, via various mechanisms, results in cell proliferation and growth.[1] In addition to androgens, growth and proliferation of the prostatic stroma is mediated by estrogens, particularly estradiol acting at the ERα estrogen receptor.[6] Estradiol is formed locally in the prostate from the conversion of testosterone by aromatase, which like 5α-reductase is localized primarily in the prostatic stroma.[7] Furthermore, as with the development of the fetal prostate, reciprocal stroma-epithelial (mesenchyme-epithelial) interactions mediated by paracrine factors, in part under the influence of androgens and estrogens, play a vital role in the growth of the prostate.[1] Following the spike in androgen levels during puberty, circulating androgen levels stabilize around 20 y of age. Stabilization of androgen levels corresponds to a period of slow prostatic growth until approximately the age of 50.[8]

Innervation of the Adult Prostate Gland

Intact neuronal inputs and contractile mechanisms of prostatic smooth muscle are essential for the proper functioning of the prostate, as sympathetically mediated contractions of the prostatic smooth muscle expel prostatic fluid from the prostate into the ejaculate. The prostate is innervated by a rich supply of mixed autonomic postganglionic neurons that arise from the pelvic (inferior hypogastric) plexus, containing neuronal inputs from both sympathetic and parasympathetic neurons. The preganglionic sympathetic neurons arise from the lumbar spinal cord and descend to the pelvic plexus via the hypogastric nerve, whereas preganglionic parasympathetic neurons join the pelvic plexus from the pelvic nerve arising from the sacral spinal cord segment.[9,10]

Consistent with the role of adrenergic nerves mediating contraction of the prostatic smooth muscle, the prostatic stroma is richly innervated with short noradrenergic nerves arising from the pelvic plexus that are absent from the prostatic glandular epithelium.[11] In the prostate, noradrenaline released from noradrenergic nerves activates G protein-coupled α_1-adrenoceptors, which results in smooth muscle contraction via an increase in intracellular calcium. In early in vitro contractile studies, prostatic smooth muscle contraction could be elicited by exogenously applied α-adrenoceptor agonists and such effects could be inhibited or blocked by non-specific α-adrenoceptor antagonists such as phentolamine (inhibits α-adrenoceptors but exhibits no selectivity toward α_1- or α_2-adrenoceptors)[12,13] or non-specific α_1-adrenoceptor antagonists such as prazosin (inhibits α_1-adrenoceptors but exhibits no selectivity toward α_{1A}-, α_{1B} or α_{1D}-adrenoceptor subtypes).[14] As delineated by molecular and cloning studies, the α_1-adrenoceptor family consists of three subtypes: the α_{1A}-adrenoceptor, the α_{1B}-adrenoceptor and the α_{1D}-adrenoceptor.[15] Experiments investigating mRNA expression and α_1-adrenoceptor density have indicated that the α_{1A}-adrenoceptor is the dominant subtype expressed in the prostate of various species, including humans, and that the α_{1A}-adrenoceptor is primarily localized to the prostatic stroma.[16,17] Pharmacological characterization studies have identified that a functional phenotype of the α_{1A}-adrenoceptor subtype, the α_{1L}-adrenoceptor, mediates the adrenergic contractile response in the human,[18,19] canine,[20] rabbit,[21] guinea pig,[22] rat[23] and mouse[24] prostates, with the α_{1B}-adrenoceptor and α_{1D}-adrenoceptor subtypes having little or no involvement in smooth muscle contraction.[19,25,26] Importantly, α_{1L}-adrenoceptors also mediate the contractile response to endogenously released noradrenaline in electrical field stimulation experiments.[19,27]

In prostatic smooth muscle, stimulation of the $G_{q/11}$ protein-coupled α_{1A}-adrenoceptors (α_{1L}-adrenoceptors) results in the prototypical activation of phospholipase C and the subsequent production of the second messengers inositol-1,4,5-triphosphate and diacylglycerol. These in turn mediate smooth muscle contraction via activation of Ca^{2+}-dependent and Rho kinase-dependent Ca^{2+}-sensitization signaling pathways.[28] However, recent studies have shown that activation of c-jun N-terminal kinase[29] as well as phosphorylation of caldesmon[30] are involved in smooth muscle contraction of the prostate following α_1-adrenoceptor stimulation, indicating that further intracellular pathways are involved in α_1-adrenoceptor mediated contraction of the prostate.

In addition to α_{1A}-adrenoceptors, which directly mediate prostatic smooth muscle contraction, both α_2-adrenoceptors and β-adrenoceptors are also found in the prostate. The human prostate contains a population of α_2-adrenoceptors with a density comparable to[31] or lesser than that of α_1-adrenoceptors[25,32] and are localized primarily in the glandular epithelium and vascular tissue with sparse stromal distribution.[32,33] Functionally, α_2-adrenoceptors reduce nerve-mediated contractions of the prostate via pre-junctional inhibition of neuronal noradrenaline release[19,31] and appear to be without a direct post-junctional role in contraction of the prostate.[25,34] Similarly, β-adrenoceptors have been found in the human, pig and rat prostates[35-37] and have been shown to inhibit α_1-adrenoceptor-mediated contractile responses in various experimental species as well as in the human prostate.[36,38-41] β-adrenoceptors inhibit α_1-adrenoceptor-mediated contraction via post-junctional activation of adenylate cyclase and accumulation of cyclic adenosine monophosphate (cAMP) resulting in relaxation of prostatic smooth muscle.[39] This response is most likely mediated by β_2-adrenoceptors; however β_1-adrenoceptors and β_3-adrenoceptors have also been implicated.[37,38,40] Recently, further interplay between α_1-adrenoceptors and β-adrenoceptors in the prostate has been proposed, as activation of α_1-adrenoceptors results in the phosphorylation of β-adrenoceptors, possibly via mechanisms involving G protein-coupled receptor kinases. Such an effect may enhance the α_1-adrenoceptor-mediated contractile response.[42]

In addition to mediating contraction, adrenergic innervation plays a role in the growth of the prostate. In rodents, sympathectomy of the hypogastric nerve causes a reduction in prostatic weight in rats,[43] whereas chronic administration of α_1-adrenoceptor agonists induces proliferation and hyperplasia.[44,45] Multiple α_1-adrenoceptor antagonists have been shown to suppress stromal and epithelial cell growth in cell culture;[46]

however this does not appear to be the result of specific blockade of the receptor and does not appear to translate to a clinical reduction in prostate volume.[47] In the rat, prostatic hyperplasia induced by phenylephrine activation of α_1-adrenoceptors has been strongly linked to activation of inflammatory pathways and the transforming growth factor β (TGFβ) signaling cascade.[45] Furthermore, human studies have shown that α_1-adrenoceptors in the prostate couple to non-contractile intracellular protein kinases involved in growth, proliferation and apoptosis,[48] indicating that activation of α_1-adrenoceptors in the human prostate couple to multiple pathways, some of which may be involved in proliferation and growth of the prostate.

Cholinergic innervation is found in both the stromal and glandular epithelial regions of the human,[11,49,50] guinea pig[27] and rat[51] prostates. Responses elicited by cholinergic innervation in the prostate are mediated by G protein-coupled muscarinic receptors of which there are five subtypes. These are the M_1, M_3 and M_5 muscarinic receptors, which couple to $G_{q/11}$ proteins, and the M_2 and M_4 muscarinic receptors, which couple to $G_{i/o}$ proteins.[52] The endogenous agonist for all five subtypes is acetylcholine.[52] In various species, muscarinic receptors are primarily localized in the glandular epithelium; however some muscarinic receptor expression is also found in the prostatic stroma suggesting a dual role in secretion and contraction. In agreement with the primary localization of muscarinic receptors on the glandular epithelium, stimulation of the cholinergic nerves or direct activation of muscarinic receptors results in the production of prostatic secretions.[53,54]

Despite muscarinic receptors being located primarily in the glandular epithelium, they play a direct role in post-junctional contraction in the prostate, as in vitro contraction of isolated prostates elicited by electrical field stimulation or exogenous agonists can be inhibited by muscarinic receptor antagonists in the human,[12,31,55] canine,[41,56] rabbit,[57,58] guinea pig,[38,58,59] rat[58,59] and mouse[60,61] prostates. However, the magnitude of cholinergic contractions in the prostate is less than that observed for α_1-adrenoceptor stimulation.[62] Additionally, muscarinic receptors regulate nerve mediated contractions by pre-junctional inhibition[31] or facilitation[63] of neurotransmitter release. The muscarinic receptor subtype responsible for contraction differs between species. M_2 muscarinic receptors mediate contraction in the canine prostate[56] and are also the predominant subtype in human stromal cells where they inhibit the accumulation of cAMP.[64] In the guinea pig prostate, M_1 muscarinic receptors facilitate nerve mediated contraction,[63] whereas contraction of the rat and mouse prostates is mediated by M_3 muscarinic receptors,[61,65] which are localized on the prostatic smooth muscle.[51]

In the prostate, activation of muscarinic receptors would likely result in the activation of the prototypical signaling pathways which are phospholipase C for M_1, M_3 and M_5 and adenylate cyclase for M_2 and M_4 muscarinic receptors, respectively. Only a few studies have investigated the signaling pathways for the muscarinic receptor subtypes, which mediate prostatic contraction. Studies in cancer cell lines indicate that activation of the muscarinic receptors present in prostate smooth muscle can result in cAMP accumulation or phosphatidylinositol turnover.[64] However, recently, Rho kinase-dependent Ca^{2+} sensitization signaling pathways have been implicated in the muscarinic receptor-mediated contraction of the rat prostate.[66]

As is the case in most physiological systems, the sympathetic and parasympathetic nervous systems appear to oppose each other in the form of a physiological balancing mechanism. This appears to be the case also in the control of prostatic growth as parasympathectomy in rats leads to increased prostate weight.[43]

In addition to adrenergic and cholinergic innervation numerous other non-adrenergic, non-cholinergic neurotransmitters that can elicit or modulate contraction are found in the prostate. While these mechanisms have been shown to play a role in prostate contraction, their physiological role is uncertain and in general their contribution to physiological contraction is much less than that of noradrenaline acting at α_{1A}-adrenoceptors.

Adenosine 5'-triphosphate (ATP) is a known sympathetic co-transmitter with noradrenaline in rat and guinea pig prostates and mediates contraction via post-junctional P2X1 purinoceptors,[27,38,67,68] localized on the prostatic smooth muscle.[67-69] However, this effect seems to be species-dependent as ATP does not contribute to nerve mediated contractile responses in the mouse prostate[60,70] despite immunolocalization of P2X1-purinoceptors in the prostatic smooth muscle.[70] Following neuronal release, ectonucleotidases hydrolyse ATP to adenosine, which in turn can activate adenosine receptors. In the mouse prostate, pre-junctional A_{2A} adenosine receptors contribute to nerve mediated contraction by facilitating noradrenaline release[71] whereas in the rat prostate, pre-junctional A_1 adenosine receptors inhibit excitatory neurotransmitter release.[72] Furthermore, A_1 and A_{2A} adenosine receptors have a post-junctional role in contraction as the α_1-adrenoceptor-mediated response in cultured human prostatic stromal cells is enhanced or inhibited by A_1 or A_{2A} adenosine receptors via the inhibition and stimulation of adenylate cyclase, respectively.[73]

Neuropeptide Y is co-localized in all adrenergic nerves in pelvic ganglia and is also found co-localized in some cholinergic nerves.[10] Dense neuropeptide Y innervation is found throughout the prostatic stroma of humans,[50] guinea pigs, rats[74] and mice.[70,75] However, there are conflicting reports concerning the expression of neuropeptide Y receptors in the prostates of humans[76] and rats.[77] Curiously, despite dense innervation to the stroma and roles in modulating neurotransmitter release in other genitourinary tissues, most studies have found that neuropeptide Y does not appear to regulate or mediate contraction of the prostate[63,76,78] and may therefore instead be involved in prostate growth.[79] However, one study did find that in the human prostate, exogenous application of high concentrations of neuropeptide Y inhibits nerve-mediated contractions and relaxes noradrenaline pre-contracted prostate preparations.[80]

In various species the prostate receives a rich supply of vasoactive intestinal polypeptide (VIP) containing nerves, which are co-localized predominantly in cholinergic nerves innervating the prostatic glandular epithelium.[10,11,75] Receptors for VIP have been found in the prostate;[81] however due to their glandular distribution, VIP does not appear to be involved in contraction and instead may have roles in secretion or prostatic growth.[82]

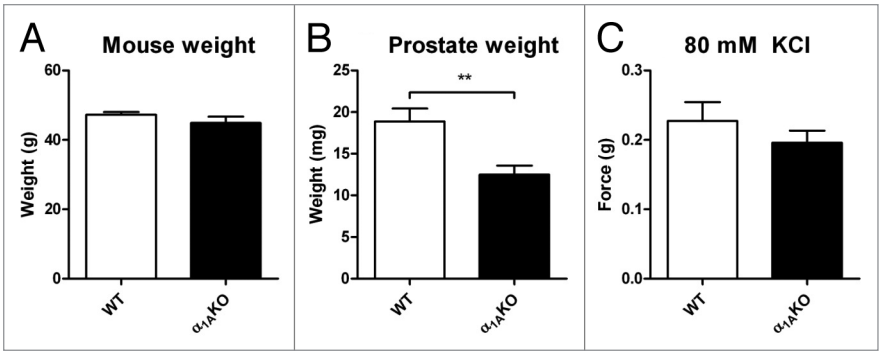

Figure 1. Aged α_{1A}KO mice. Comparison of mean mouse weight (**A**), isolated prostate weight (**B**) and mean contractile response to 80 mM KCl Krebs-Henseleit solution (**C**) from aged wild-type (WT, open columns) and α_{1A}-adrenoceptor knockout mice (α_{1A}KO, black columns). Columns represent mean weight/contractile force ± S.E.M., n = 10–14. p-values, **p < 0.01 vs. control, were calculated by an unpaired t-test and represent the probability of genotype affecting prostate weight in the aged mouse.

In contrast to neuropeptide Y and VIP, which have little if any role in the contraction of the prostate, other peptides are known to regulate or elicit prostatic contraction. The sensory neuropeptide calcitonin gene-related peptide (CGRP) has been found in nerves located within the stroma and/or glandular epithelium of numerous species[70,80,83-85] as well as neuroendocrine cells in the human prostate.[86] Functionally, exogenous CGRP has been shown to relax phenylephrine mediated contractions[78] or inhibit nerve mediated contractions[87] in the rat prostate. Furthermore, tachykinins also modulate prostate contraction. Neurokinin A and substance P have been found distributed sparsely in nerve fibers supplying the prostatic smooth muscle of human,[50] sheep,[88] canine,[85] guinea pig, rat[89,90] and mouse prostates.[70] Exogenous application of tachykinin agonists induces prostate contraction via neurokinin NK2 receptors in the human prostate,[91] whereas neurokinin NK1 and NK2 receptors mediate contraction to exogenous agonists in cultured canine prostatic stromal cells.[85] Conversly, no direct contractile effects have been observed in the rat[78] or pig[58] prostates in response to substance P. In the guinea pig prostate, however, substance P and neurokinin A potentiate contractions elictited by nerve stimulation.[90]

While not mediating contraction, nitrergic neuronal mechanisms regulate the tone of the prostatic smooth muscle by mediating relaxation. The prostate receives a dense innervation of nitric oxide synthase containing nerves, which are localized throughout the prostatic stroma and glandular epithelium.[92] In addition, nitric oxide synthase is commonly co-localized in both noradrenergic and cholinergic nerves.[80,84] Electrical field stimulation relaxes in vitro prostate preparations that have been pre-contracted with noradrenaline in the human, canine,[93] rabbit[58,94] and guinea pig[58] tissue. This nerve-mediated relaxation can be blocked by inhibition of nitric oxide synthase or enhanced in the presence of nitric oxide donors.[58,93,94] The exogenous addition of nitric oxide donors also relaxes precontracted prostate tissues.[58,80,93,95] Furthermore, when the adrenergic and cholinergic components of nerve mediated contraction are blocked, electrical field stimulation relaxes prostatic smooth muscle, which can be inhibited or enhanced by nitric oxide synthase inhibitors or nitric oxide donors, respectively.[93] Phosphodiesterase (PDE) enzymes, which are involved in the hydrolysis of cyclic nucleotides produced by the action of nitric oxide, are also found in the human prostate.[95] Moreover, inhibitors of the PDE4 and PDE5 isoforms have been shown to relax prostatic tissues precontracted with noradrenaline or endothelin-1.[95]

Age-Related Changes in Prostate Innervation

At approximately age 50, the steady growth of the prostate slowly accelerates.[8] In parallel, a number of studies have shown an age-related decrease in the innervation to the prostate over this time.[50,96] At the same time, an increase in α_{1A}-adrenoceptor mRNA expression has been observed in aged human prostate.[97,98] This is in contrast to the aged rat prostate where α_{1A}-adrenoceptor mRNA expression is lower.[99] In the aged human prostate the contractile response to exogenously adminstered α_1-adrenoceptor agonists remains the same[36] or is increased.[55] However, in similar studies of the aged rat prostate, a decrease in α_1-adrenoceptor density[99] and distribution[33] was observed, which resulted in a reduced contractile response mediated by α_1-adrenoceptor agonists.[99] While the reason for the difference between species is unclear, it might be due to differences in age. Rats used in the previous studies were 18–22 mo of age, corresponding to an approximate human age of only 45–55 y old.[100]

Research in our laboratory has also noted that prostates taken from 12-mo-old α_{1A}-adrenoceptor knockout mice are smaller than those taken from wild-type litter mate controls at the same age (**Fig. 1**). As previously mentioned, sympathetic innervation is known to play a role in the growth of the rat prostate, as surgical sympathectomy of the pelvic ganglia[43] reduces the size of the prostate, while sympathetic stimulation results in prostate growth.[44] Furthermore, in patients with spinal cord injury resulting in severe paralysis, smaller prostate size is observed.[101] In rats, the in vivo administration of non-selective α_1-adrenoceptor antagonists results in a reduction in prostatic weight[102] as well as cellular proliferation.[103] This effect appears to be dose dependent, as low doses of α_1-adrenoceptor antagonist have no effect on prostatic weight.[104] Our observations with knockout mice (**Fig. 1**) indicate that the α_{1A}-adrenoceptor subtype is not only responsible for the nerve mediated contractile response but in the mouse prostate is responsible for sympathetically mediated growth as well.

Cholinergic innervation of the human prostate was shown not to change with age.[96] Similarly, in the aged human prostate[31] as well as the aged canine[105] and rabbit[106] prostates, no change in muscarinic receptor density was observed. Whereas, in the aged rat prostate, M_{1-3} muscarinic receptor mRNA decreased[107] as did M_3 muscarinic receptor density.[65,107] However, studies using antibodies in the rat prostate, showed an increase in M_2 muscarinic receptors in the rat prostate with age.[33] Therefore the effect of age on the cholinergic innervation in the aged prostate appears to be

highly subtype and species dependent. This is of note as a possible synergistic adrenergic-cholinergic action has previously been observed in the human prostate.[31]

Many inhibitory mechanisms of prostate contractility have also been studied with regard to aging. An increase in α_2-adrenoceptor density has been observed with age in the human,[25] rat[33] and rabbit[106] prostates. In the prostate, α_2-adrenoceptors are primarily responsible for inhibition of noradrenaline release and do not play a direct contractile role,[17] therefore, the implications of this phenomenon are unknown and could be complex. Expression of β-adrenoceptors, which are capable of relaxing electrical field stimulation and agonist mediated contraction,[17] have also been shown to be reduced in the aged rat prostate.[33] Furthermore, a decrease in the activity of adenylate cyclase activated by the β-adrenoceptor agonist isoproterenol occurs in the aged rat prostate.[108] In contrast, β-adrenoceptor expression does not change in the aged rabbit prostate.[106] Additionally, nitrergic innervation and nitric oxide mediated relaxation is decreased in the aged rabbit[94] and guinea pig[109] prostates. Therefore, a reduction in the inhibitory mechanisms of contraction in the prostate with age may play a role in the development of lower urinary tract symptoms (LUTS) associated with BPH.

BPH

BPH is a consequence of age- and androgen-dependant growth of the human prostate and affects approximately 50% of men by the age of 60 and 90% by 90 y of age.[2] BPH is a purely histological description of the prostate and should not be confused with LUTS associated with or secondary to BPH.[110] While rarely life threatening, LUTS affect approximately 50% of men aged 50 to 80 y[111] and refers to a number of symptoms that can be found in either men or women that can severely affect their quality of life.[112] LUTS may be caused by BPH, however other factors such as detrusor over- or under-activity may also result in such symptoms.[113] The LUTS can be categorized as related to urine storage, urine voiding and post-micturition. Urine storage symptoms relate to urgency and frequency of urination, nocturia and incontinence. Urine voiding-related symptoms include hesitancy, poor flow, intermittency and straining, while post-micturition symptoms include post-void dribble and a sense of incomplete emptying.[110] Due to the high prevalence of LUTS accompanying BPH, there are significant costs associated with treatment that may be expected to rise with the aging population.[114]

BPH is characterized by a progressive nodular increase in the number of epithelial and stromal cells, which occurs initially in the transition and periurethral zones of the human prostate.[115] Hyperplasia of the stoma is predominant and results in a greater proportion of smooth muscle relative to the glandular epithelium and an increase in the muscular tone of the hyperplasic prostate.[116] BPH can lead to benign prostatic enlargement and in turn benign prostatic obstruction of the urethra. Benign prostatic obstruction is one cause of bladder outlet obstruction; others include bladder neck obstruction and urethral stricture,[117] which increases bladder pressure and increases urethral resistance impairing the flow of urine from the bladder, leading to the voiding symptoms associated with LUTS.[118] Bladder outlet obstruction due to BPH may also result in storage symptoms by inducing overactivity of the bladder detrusor.[119]

Effects of BPH on Prostate Innervation

In parallel with BPH development, α_1-adrenoceptor density in the human hyperplasic prostate is increased[120] or remains the same as the normal prostate.[25,36] Consequently there is an increase in the tone of the prostatic smooth muscle, which constricts the urethra, contributing to the LUTS associated with BPH. In the hyperplasic prostate the increase in tone of the prostate is mediated, in part, by neuronal noradrenaline acting at α_{1L}-adrenoceptors to cause smooth muscle contraction and this mechanism forms the basis for the treatment of BPH with α_1-adrenoceptor antagonists. However, prostatic smooth muscle contraction is also mediated by numerous other receptor systems,[74,121] such as acetylcholine acting at muscarinic receptors or ATP acting at purinoceptors. Therefore, blockade of these receptors, particularly muscarinic receptors, has been hypothesized as a suitable additional target for a better pharmacological treatment for BPH.[122] Changes with age in these, or other mediators of prostatic smooth muscle contraction, may play a role in the development of LUTS associated with BPH by increasing prostatic tone.

Given the important role of α_1-adrenoceptors in the treatment of BPH, many studies have previously investigated the effect of age or disease on adrenergic contractile mechanisms, which demonstrated significant variation between species and experimental conditions. In BPH as with age, total innervation as well as adrenergic innervation of the human prostate gland decreases.[50,96] Adrenoceptor studies of the human prostate show contrasting effects. α_{1A}-adrenoceptor mRNA was increased in the diseased human prostate,[97] as was observed with age in normal human prostate.[98] At the receptor level, α_1-adrenoceptor density in the hyperplasic human prostate is increased[120] or remains the same as in normal prostate.[25,36] Studies of the contractile response in human prostate mirror those investigating α_1-adrenoceptor density. Whereby, the contractile response of human hyperplasic prostate to exogenously applied α_1-adrenoceptor agonists were shown to remain the same[31,36,55] or were increased[31] compared with normal prostate.

In contrast to the adrenergic component of contraction, only a few studies have investigated the effect of age or disease on the cholinergic component of contraction in the prostate. As observed with the adrenergic component, previous studies show differences between species and experiments. Unlike in normal aged prostates, in hyperplasic prostates, acetylcholinesterase staining decreased.[49,50] However, as seen in the aged prostate, hyperplasic human prostate[31] shows no change in muscarinic receptor density. Conversely, an upregulation of the M_3 muscarinic receptor, but not the M_1 or M_2 muscarinic receptor subtypes, was observed in the human hyperplasic prostate.[123] Finally, acetylcholine was shown to potentate the noradrenergically mediated contractile response in the hyperplasic human prostate,[31] but not in un-diseased tissue.[31] In general, the effect

of BPH on the cholinergic contractile response in the prostate gland is still poorly understood.

Changes in inhibitory inputs of prostatic contraction have also been widely investigated with respect to BPH. Expression of β-adrenoceptors, which are capable of relaxing electrical field stimulation and agonist mediated contraction,[17] were shown to be decreased in the hyperplasic human prostates.[36] Furthermore, a decrease in the activity of adenylate cyclase activated by the β-adrenoceptor agonist isoproterenol occurs in the hyperplasic human prostate.[36] These studies implicate a reduction in the β-adrenoceptor inhibitory mechanisms of contraction in the prostate as playing a role in the development of LUTS associated with BPH. In contrast, in the hyperplasic human prostate expression of α_2-adrenoceptors was shown to be increased.[25,31]

Prostate Cancer

Approximately 20,000 men are diagnosed with localized (organ-confined) prostate cancer in Australia each year. In many patients the tumors are slow-growing and are not associated directly with mortality. Therefore these men can be successfully treated with conventional treatment regimes including surgical removal of the prostate (radical prostatectomy) or radiotherapy. If the patient relapses and the cancer returns, they are treated with androgen ablation/deprivation therapy, which can reduce the tumor and circulating prostate specific antigen (PSA) to undetectable levels. However, in most cases the cancer will eventually recur in an androgen independent/hormone refractory/castration resistant form that usually results in lethal bone metastasis.[124] Chemotherapeutic regimes for advanced prostate cancer are often still used but generally result in only a small increase in survival time.[125,126]

The strongest risk factor for the development of prostate cancer in men is age. The chance of developing the disease rises rapidly after the age of 50 with 1 in 11 Australian men developing prostate cancer by the age of 70. The sympathetic nervous system is implicated in disorders of the aging male such as hypertension and BPH. In both of these age-related disorders, the sympathetic nervous system shows signs of overactivity and symptoms can be controlled by the use of therapeutic drugs which block the effects mediated by adrenoceptors (e.g., α_1-adrenoceptor antagonists, β-blockers).

In humans, α_1-adrenoceptor antagonists used in the treatment of BPH have been shown to induce prostate apoptosis.[98,103,127] This apoptotis inducing effect of α_1-adrenoceptor antagonists has also been shown in prostate cancer cell lines in vitro[46,128,129] and in vivo in mice bearing a tumor following subcutaneous xenograft injection of PC3[128] or LNCaP[129] cells. The antitumorigenic effect of the α_1-adrenoceptor antagonists was originally postulated to be due to antiangiogenic effects on the prostate vasculature;[130] however, their apoptotic effects on prostate cancer cell lines in culture[46,128] suggest an alternate mechanism of action. Nevertheless, several reports indicate that only the quinazoline based α_1-adrenoceptor antagonists have antiapoptotic efficacy against prostate cancer cells and that this is by an α_1-adrenoceptor-independent mechanism.[130] However, in vivo data generated from our laboratory using α_{1A} adrenoceptor knockout mice indicates that there is also a mechanism which involves the sympathetic nervous system and more specifically α_1-adrenoceptors (**Fig. 1**). In support of this, it has previously been shown that activating the α_1-adrenoceptor signaling pathway induces proliferation of human prostatic stromal cells.[131]

β-adrenoceptors have also been implicated in metastasis development in models of prostate and other cancers. In vitro studies have shown that active migration of tumor cells can be induced by noradrenaline using cell lines derived from colon, breast or prostate cancer cells.[132] Furthermore, this tumor cell migration could be inhibited by the β-adrenoceptor antagonists propranolol or ICI 118,551.[132] Noradrenaline induced development of metastasis following in vivo xenograft of PC3 cells in BALB/c nude mice can also be inhibited by the β-blocker propranolol.[133] Indeed it has recently been shown that inducing stress in an in vivo mouse xenograft model of prostate cancer can artificially activate the sympathetic nervous system to stimulate β-adrenoceptor induced metastatic effects.[134] This metastatic effect was mediated by increased levels of circulating adrenaline and could be inhibited by β-adrenoceptor antagonists. With regard to parasympathetic cholinergic mechanisms, stimulation of muscarinic receptors of the M_3 subtype have been shown to stimulate proliferation of LNCaP prostate cancer cells as well as benign and cancerous primary prostate cells.[135] Similarly, in studies of the cancerous rat prostate, an increase in M_3 muscarinic receptor density was observed.[136] This suggests that M_3 muscarinic receptors may play a significant role in prostate cancer tumor growth and possibly also androgen-independent tumor progression.

It has previously been hypothesized that there is an association between increased sympathetic activity and prostate cancer,[137] and the scientific literature abounds with circumstantial evidence for the involvement of the sympathetic nervous system in prostate cancer progression. For instance obesity, which is associated with high sympathetic tone,[138] is also associated with increased prostate cancer risk,[139] as is cardiovascular disease.[140,141] In clinical studies on schizophrenia patients, there is a significant association of reduced risk of prostate cancer among patients treated with neuroleptic medication,[142] particularly those who had been treated with high dose phenothiazine neuroleptics such as chlorpromazine.[142] Although these drugs primarily target dopamine receptors, high doses of this class of neuroleptics are known to antagonize α_1-adrenoceptors, so it is notable that this relationship was seen only in patients treated with a high cumulative dose. Diabetes, on the other hand, which is associated with sympathetic neuropathy, is associated with a lower risk for late stage prostate cancer but no association in early stages.[143] Similarly, lower body sympathetic dysfunction due to spinal cord injury is associated with a low incidence of prostate cancer diagnosis.[144] Finally, the most striking clinical evidence comes from a study on antihypertensives which indicated that β-blockers and the long-term use of α-adrenoceptor antagonists may prevent prostate cancer whereas other classes of antihypertensives such as calcium channel blockers or angiotensin-converting enzyme inhibitors do not influence prostate cancer risk.[145]

In clinical trials, a study conducted on 4,070 men in the US found that men exposed to α_1-adrenoceptor antagonists have a 1.5 times lower risk of developing prostate cancer than unexposed men.[146] This study only looked at men taking the quinazoline based antagonists doxazosin, prazosin and terazosin and therefore observed effects may be due to non-adrenoceptor mechanisms. Conversely, evidence from a larger observational cohort study of 23,320 Finnish men showed that overall prostate cancer risk, while not reduced among α-adrenoceptor antagonist users compared with non users, showed a decreased incidence of high grade tumors,[147] indicating a decrease in tumor aggression. This second study looked at the effects of the widely used sulphonamide based α_1-adrenoceptor antagonist tamsulosin as well as the quinazoline based antagonist alfuzosin. The use of the non-quinazoline tamsulosin in this study is likely to be the cause of this novel effect on tumor aggression, which is likely to be α_1-adrenoceptor mediated. The evidence found in this second epidemiological study is consistent with the sympathetic nervous system, which is often overactive in the aging male, contributing to the progression of prostate cancer. The former study, on the other hand, is consistent with the previously reported antiproliferative α_1-adrenoceptor independent effects of the quinazoline-based compounds.

Interpretation of antitumorigenic effects in prostate cancer cell lines is difficult since the expression of the different adrenoceptor and muscarinic receptor subtypes in the different prostate cancer cell lines is not well characterized. In addition, these commonly studied cell lines are likely to be phenotypically different under different conditions in differerent laboratories. For example, based on single-cell RNA sequencing data, the β_2-adrenoceptor is expressed at significant levels in the PC3 and LNCaP prostate cancer cell lines while the M_3 muscarinic receptor is expressed only in PC3 cells[148] while the α_{1A}-adrenoceptor is not expressed in either of these cell lines. However, there are inconsistencies between the sequencing data and functional studies on α_{1A}-adrenoceptors and muscarinic receptors. Two papers have suggested a role for the α_{1A}-adrenoceptor in proliferation of LNCaP cells[149] and chemoresistance of DU145 cells;[150] however receptor detection was based on α_{1A}-drenoceptors antibodies, which are notorious for lack of specificity.[151] The muscarinic receptor agonist carbachol likewise stimulates proliferation of LNCaP cells despite an apparent lack of mRNA for any of the relevant acetylcholine receptor subtypes.[135]

Conclusions

Prostate disease and autonomic nervous system activity appear to change with age in a parallel and similar manner. Further research into whether this association is coincidental or not may elucidate the physiological mechanisms involved in clinical observations such as those that show prostate cancer patients who have been exposed to α_1-adrenoceptor antagonists for the treatment of BPH have a lower incidence of high grade tumors.[147] Validation of such a physiological mechanism will indicate a novel molecular target for chemotherapy of metastatic androgen-independent prostate cancer. This will in turn drive the development of new treatment strategies for these forms of currently treatment resistant prostate cancers. In addition, α_1-adrenoceptor antagonists, β-blockers and muscarinic receptor antagonists are already currently available, reasonably well-tolerated and very effective in the treatment of LUTS and hypertension. Understanding these signaling pathways may provide evidence for the immediate use of such a treatment strategy by clinicians to produce a survival advantage for advanced prostate cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Cunha GR, Donjacour AA, Cooke PS, Mee S, Bigsby RM, Higgins SJ, et al. The endocrinology and developmental biology of the prostate. Endocr Rev 1987; 8:338-62; PMID:3308446; http://dx.doi.org/10.1210/edrv-8-3-338
2. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132:474-9; PMID:6206240
3. McNeal JE. Normal histology of the prostate. Am J Surg Pathol 1988; 12:619-33; PMID:2456702; http://dx.doi.org/10.1097/00000478-198808000-00003
4. Bruchovsky N, Wilson JD. The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. J Biol Chem 1968; 243:2012-21; PMID:4384673
5. Fang S, Anderson KM, Liao S. Receptor proteins for androgens. On the role of specific proteins in selective retention of 17-beta-hydroxy-5-alpha-androstan-3-one by rat ventral prostate in vivo and in vitro. J Biol Chem 1969; 244:6584-95; PMID:5361546
6. Prins GS, Korach KS. The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids 2008; 73:233-44; PMID:18093629; http://dx.doi.org/10.1016/j.steroids.2007.10.013
7. Matzkin H, Soloway MS. Immunohistochemical evidence of the existence and localization of aromatase in human prostatic tissues. Prostate 1992; 21:309-14; PMID:1281323; http://dx.doi.org/10.1002/pros.2990210407
8. Swyer GI. Post-natal growth changes in the human prostate. J Anat 1944; 78:130-45; PMID:17104953
9. Keast JR. Visualization and immunohistochemical characterization of sympathetic and parasympathetic neurons in the male rat major pelvic ganglion. Neuroscience 1995; 66:655-62; PMID:7644029; http://dx.doi.org/10.1016/0306-4522(94)00595-V
10. Keast JR. Plasticity of pelvic autonomic ganglia and urogenital innervation. Int Rev Cytol 2006; 248:141-208; PMID:16487791; http://dx.doi.org/10.1016/S0074-7696(06)48003-7
11. Vaalasti A, Hervonen A. Autonomic innervation of the human prostate. Invest Urol 1980; 17:293-7; PMID:7351361
12. Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. Br J Urol 1975; 47:193-202; PMID:1148621; http://dx.doi.org/10.1111/j.1464-410X.1975.tb03947.x
13. Raz S, Zeigler M, Caine M. Pharmacological receptors in the prostate. Br J Urol 1973; 45:663-7; PMID:4775741; http://dx.doi.org/10.1111/j.1464-410X.1973.tb12237.x
14. Shapiro A, Mazouz B, Caine M. The alpha-adrenergic blocking effect of prazosin on the human prostate. Urol Res 1981; 9:17-20; PMID:6115493; http://dx.doi.org/10.1007/BF00256833
15. Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ, et al. International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. Pharmacol Rev 1995; 47:267-70; PMID:7568329
16. Testa R, Guarneri L, Ibba M, Strada G, Poggesi E, Taddei C, et al. Characterization of alpha 1-adrenoceptor subtypes in prostate and prostatic urethra of rat, rabbit, dog and man. Eur J Pharmacol 1993; 249:307-15; PMID:7904564; http://dx.doi.org/10.1016/0014-2999(93)90527-O
17. Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 2006; 147(Suppl 2):S88-119; PMID:16465187; http://dx.doi.org/10.1038/sj.bjp.0706619
18. Muramatsu I, Oshita M, Ohmura T, Kigoshi S, Akino H, Gobara M, et al. Pharmacological characterization of alpha 1-adrenoceptor subtypes in the human prostate: functional and binding studies. Br J Urol 1994; 74:572-8; PMID:7530120; http://dx.doi.org/10.1111/j.1464-410X.1994.tb09186.x

19. Guh JH, Chueh SC, Ko FN, Teng CM. Characterization of alpha 1-adrenoceptor subtypes in tension response of human prostate to electrical field stimulation. Br J Pharmacol 1995; 115:142-6; PMID:7647968; http://dx.doi.org/10.1111/j.1476-5381.1995.tb16331.x
20. Ohmura T, Sakamoto S, Hayashi H, Kigoshi S, Muramatsu I. Identification of alpha 1-adrenoceptor subtypes in the dog prostate. Urol Res 1993; 21:211-5; PMID:8102023; http://dx.doi.org/10.1007/BF00590038
21. Hiraoka Y, Ohmura T, Sakamoto S, Hayashi H, Muramatsu I. Identification of alpha 1-adrenoceptor subtypes in the rabbit prostate. J Auton Pharmacol 1995; 15:271-8; PMID:8576274; http://dx.doi.org/10.1111/j.1474-8673.1995.tb00310.x
22. Pennefather JN, Lau WA, Chin C, Story ME, Ventura S. alpha(1L)-adrenoceptors mediate noradrenaline-induced contractions of the guinea-pig prostate stroma. Eur J Pharmacol 1999; 384:25-30; PMID:10611415; http://dx.doi.org/10.1016/S0014-2999(99)00667-6
23. Hiraoka Y, Ohmura T, Oshita M, Watanabe Y, Morikawa K, Nagata O, et al. Binding and functional characterization of alpha1-adrenoceptor subtypes in the rat prostate. Eur J Pharmacol 1999; 366:119-26; PMID:10064160; http://dx.doi.org/10.1016/S0014-2999(98)00895-4
24. Gray KT, Ventura S. α_{1L}-adrenoceptors mediate contractions of the isolated mouse prostate. Eur J Pharmacol 2006; 540:155-61; PMID:16716294; http://dx.doi.org/10.1016/j.ejphar.2006.04.016
25. Chapple CR, Aubry ML, James S, Greengrass PM, Burnstock G, Turner-Warwick RT, et al. Characterisation of human prostatic adrenoceptors using pharmacology receptor binding and localisation. Br J Urol 1989; 63:487-96; PMID:2471572; http://dx.doi.org/10.1111/j.1464-410X.1989.tb05942.x
26. Chapple CR, Burt RP, Andersson PO, Greengrass P, Wyllie M, Marshall I. Alpha 1-adrenoceptor subtypes in the human prostate. Br J Urol 1994; 74:585-9; PMID:7530122; http://dx.doi.org/10.1111/j.1464-410X.1994.tb09188.x
27. Lau WAK, Ventura S, Pennefather JN. Pharmacology of neurotransmission to the smooth muscle of the rat and the guinea-pig prostate glands. J Auton Pharmacol 1998; 18:349-56; PMID:9915599; http://dx.doi.org/10.1046/j.1365-2680.1998.1860349.x
28. Christ GJ, Andersson KE. Rho-kinase and effects of Rho-kinase inhibition on the lower urinary tract. Neurourol Urodyn 2007; 26(Suppl):948-54; PMID:17696159; http://dx.doi.org/10.1002/nau.20475
29. Strittmatter F, Walther S, Gratzke C, Göttinger J, Beckmann C, Roosen A, et al. Inhibition of adrenergic human prostate smooth muscle contraction by the inhibitors of c-Jun N-terminal kinase, SP600125 and BI-78D3. Br J Pharmacol 2012; 166:1926-35; PMID:22364229; http://dx.doi.org/10.1111/j.1476-5381.2012.01919.x
30. Walther S, Strittmatter F, Roosen A, Heinzer F, Rutz B, Stief CG, et al. Expression and alpha1-adrenoceptor regulation of caldesmon in human prostate smooth muscle. Urology 2012; 79:e5-12; PMID:22197205; http://dx.doi.org/10.1016/j.urology.2011.10.053
31. Hedlund H, Andersson KE, Larsson B. Alpha-adrenoceptors and muscarinic receptors in the isolated human prostate. J Urol 1985; 134:1291-8; PMID:2414474
32. James S, Chapple CR, Phillips MI, Greengrass PM, Davey MJ, Turner-Warwick RT, et al. Autoradiographic analysis of alpha-adrenoceptors and muscarinic cholinergic receptors in the hyperplastic human prostate. J Urol 1989; 142:438-44; PMID:2473223
33. Slater M, Barden JA, Murphy CR. Tyrosine kinase A, autonomic and transmitter receptors, but not innervation, are upregulated in the aging rat prostate. Acta Histochem 2000; 102:427-38; PMID:11145535; http://dx.doi.org/10.1078/0065-1281-00565
34. Hieble JP, Caine M, Zalaznik E. In vitro characterization of the alpha-adrenoceptors in human prostate. Eur J Pharmacol 1985; 107:111-7; PMID:2579826; http://dx.doi.org/10.1016/0014-2999(85)90048-2
35. Poyet P, Gagne B, Lavoie M, Labrie F. Characteristics of the beta-adrenergic receptor in the rat ventral prostate using [125I]cyanopindolol. Mol Cell Endocrinol 1986; 48:59-67; PMID:2877909; http://dx.doi.org/10.1016/0303-7207(86)90166-8
36. Tsujii T, Azuma H, Yamaguchi T, Oshima H. A possible role of decreased relaxation mediated by beta-adrenoceptors in bladder outlet obstruction by benign prostatic hyperplasia. Br J Pharmacol 1992; 107:803-7; PMID:1282075; http://dx.doi.org/10.1111/j.1476-5381.1992.tb14527.x
37. Goepel M, Wittmann A, Rübben H, Michel MC. Comparison of adrenoceptor subtype expression in porcine and human bladder and prostate. Urol Res 1997; 25:199-206; PMID:9228673; http://dx.doi.org/10.1007/BF00941983
38. Haynes JM, Hill SJ. Beta-adrenoceptor-mediated inhibition of alpha 1-adrenoceptor-mediated and field stimulation-induced contractile responses in the prostate of the guinea pig. Br J Pharmacol 1997; 122:1067-74; PMID:9401771; http://dx.doi.org/10.1038/sj.bjp.0701494
39. Drescher P, Eckert RE, Madsen PO. Smooth muscle contractility in prostatic hyperplasia: role of cyclic adenosine monophosphate. Prostate 1994; 25:76-80; PMID:7518597; http://dx.doi.org/10.1002/pros.2990250204
40. Kalodimos PJ, Ventura S. Beta2-adrenoceptor-mediated inhibition of field stimulation induced contractile responses of the smooth muscle of the rat prostate gland. Eur J Pharmacol 2001; 431:81-9; PMID:11716846; http://dx.doi.org/10.1016/S0014-2999(01)01414-5
41. Normandin DE, Lodge NJ. Pharmacological characterization of the isolated canine prostate. J Urol 1996; 155:1758-61; PMID:8627879; http://dx.doi.org/10.1016/S0022-5347(01)66193-7
42. Hennenberg M, Strittmatter F, Walther S, Hedlund P, Andersson KE, Stief CG, et al. α1-adrenoceptor activation induces phosphorylation of β2-adrenoceptors in human prostate tissue. BJU Int 2011; 108:922-8; PMID:21371241
43. McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the rat prostate gland is facilitated by the autonomic nervous system. Biol Reprod 1994; 51:99-107; PMID:7918880; http://dx.doi.org/10.1095/biolreprod51.1.99
44. Golomb E, Kruglikova A, Dvir D, Parnes N, Abramovici A. Induction of atypical prostatic hyperplasia in rats by sympathomimetic stimulation. Prostate 1998; 34:214-21; PMID:9492850; http://dx.doi.org/10.1002/(SICI)1097-0045(19980215)34:3<214::AID-PROS9>3.0.CO;2-H
45. Kim J, Yanagihara Y, Kikugawa T, Ji M, Tanji N, Masayoshi Y, et al. A signaling network in phenylephrine-induced benign prostatic hyperplasia. Endocrinology 2009; 150:3576-83; PMID:19443575; http://dx.doi.org/10.1210/en.2008-1782
46. Kyprianou N, Benning CM. Suppression of human prostate cancer cell growth by α1-adrenoceptor antagonists doxazosin and terazosin via induction of apoptosis. Cancer Res 2000; 60:4550-5; PMID:10969806
47. Roehrborn CG. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate Cancer Prostatic Dis 2006; 9:121-5; PMID:16304557; http://dx.doi.org/10.1038/sj.pcan.4500849
48. Kanagawa K, Sugimura K, Kuratsukuri K, Ikemoto S, Kishimoto T, Nakatani T. Norepinephrine activates P44 and P42 MAPK in human prostate stromal and smooth muscle cells but not in epithelial cells. Prostate 2003; 56:313-8; PMID:12858360; http://dx.doi.org/10.1002/pros.10267
49. Dunzendorfer U, Jonas D, Weber W. The autonomic innervation of the human prostate. Histochemistry of acetylcholinesterase in the normal and pathologic states. Urol Res 1976; 4:29-31; PMID:59994; http://dx.doi.org/10.1007/BF00256133
50. Chapple CR, Crowe R, Gilpin SA, Gosling J, Burnstock G. The innervation of the human prostate gland--the changes associated with benign enlargement. J Urol 1991; 146:1637-44; PMID:1719253
51. Nadelhaft I. Cholinergic axons in the rat prostate and neurons in the pelvic ganglion. Brain Res 2003; 989:52-7; PMID:14519511; http://dx.doi.org/10.1016/S0006-8993(03)03353-5
52. Caulfield MP, Birdsall NJM. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998; 50:279-90; PMID:9647869
53. Smith ER. The stimulation of canine prostatic secretion by parasympathomimetic agents. J Pharmacol Exp Ther 1968; 164:312-6; PMID:5699092
54. Smith ER, Lebeaux MI. The mediation of the canine prostatic secretion provoked by hypogastric nerve stimulation. Invest Urol 1970; 7:313-8; PMID:4392480
55. Gup DI, Shapiro E, Baumann M, Lepor H. Contractile properties of human prostate adenomas and the development of infravesical obstruction. Prostate 1989; 15:105-14; PMID:2477832; http://dx.doi.org/10.1002/pros.2990150204
56. Fernández JLG, Rivera L, López PG, Recio P, Vela-Navarrete R, García-Sacristán A. Characterization of the muscarinic receptor mediating contraction of the dog prostate. J Auton Pharmacol 1998; 18:205-11; PMID:9788290; http://dx.doi.org/10.1046/j.1365-2680.1998.18486.x
57. Seki N, Suzuki H. Electrical and mechanical activity of rabbit prostate smooth muscles in response to nerve stimulation. J Physiol 1989; 419:651-63; PMID:2621646
58. Najbar-Kaszkiel AT, Di Iulio JL, Li CG, Rand MJ. Characterisation of excitatory and inhibitory transmitter systems in prostate glands of rats, guinea pigs, rabbits and pigs. Eur J Pharmacol 1997; 337:251-8; PMID:9430422; http://dx.doi.org/10.1016/S0014-2999(97)01270-3
59. Cohen ML, Drey K. Contractile responses in bladder body, bladder neck and prostate from rat, guinea pig and cat. J Pharmacol Exp Ther 1989; 248:1063-8; PMID:2539454
60. White CW, Short JL, Haynes JM, Evans RJ, Ventura S. The residual nonadrenergic contractile response to nerve stimulation of the mouse prostate is mediated by acetylcholine but not ATP in a comparison with the mouse vas deferens. J Pharmacol Exp Ther 2010; 335:489-96; PMID:20724483; http://dx.doi.org/10.1124/jpet.110.172130
61. White CW, Short JL, Haynes JM, Matsui M, Ventura S. Contractions of the mouse prostate elicited by acetylcholine are mediated by M(3) muscarinic receptors. J Pharmacol Exp Ther 2011; 339:870-7; PMID:21885618; http://dx.doi.org/10.1124/jpet.111.186841
62. Ventura S, Pennefather JN, Mitchelson F. Cholinergic innervation and function in the prostate gland. Pharmacol Ther 2002; 94:93-112; PMID:12191596; http://dx.doi.org/10.1016/S0163-7258(02)00174-2
63. Lau WAK, Pennefather JN, Mitchelson FJ. Cholinergic facilitation of neurotransmission to the smooth muscle of the guinea-pig prostate gland. Br J Pharmacol 2000; 130:1013-20; PMID:10882385; http://dx.doi.org/10.1038/sj.bjp.0703409
64. Yazawa H, Saita Y, Iida E, Honma Y, Morita T, Honda K. Characterization of muscarinic cholinoceptor in primary culture of smooth muscle cells from human prostate. J Urol 1994; 152:2173-7; PMID:7966710
65. Yazawa H, Honda K. The M3-muscarinic cholinoceptor subtype in rat prostate and its down regulation by aging. Jpn J Pharmacol 1993; 61:319-24; PMID:8320877; http://dx.doi.org/10.1254/jjp.61.319

66. Saito M, Ohmasa F, Shomori K, Dimitriadis F, Ohiwa H, Shimizu S, et al. Rhos and Rho kinases in the rat prostate: their possible functional roles and distributions. Mol Cell Biochem 2011; 358:207-13; PMID:21720764; http://dx.doi.org/10.1007/s11010-011-0936-9
67. Ventura S, Dewalagama RK, Lau LCL. Adenosine 5'-triphosphate (ATP) is an excitatory cotransmitter with noradrenaline to the smooth muscle of the rat prostate gland. Br J Pharmacol 2003; 138:1277-84; PMID:12711628; http://dx.doi.org/10.1038/sj.bjp.0705167
68. Buljubasich R, Ventura S. Adenosine 5'-triphosphate and noradrenaline are excitatory cotransmitters to the fibromuscular stroma of the guinea pig prostate gland. Eur J Pharmacol 2004; 499:335-44; PMID:15381056; http://dx.doi.org/10.1016/j.ejphar.2004.07.080
69. Lee HY, Bardini M, Burnstock G. P2X receptor immunoreactivity in the male genital organs of the rat. Cell Tissue Res 2000; 300:321-30; PMID:10867827; http://dx.doi.org/10.1007/s004410000207
70. Gray KT, Ventura S. Evaluation of the mouse prostate as a suitable model for the study of human prostate function. J Pharmacol Toxicol Methods 2005; 51:41-50; PMID:15596113; http://dx.doi.org/10.1016/j.vascn.2004.07.001
71. Gray KT, Short JL, Ledent C, Ventura S. Targeted disruption of the A2A adenosine receptor reduces in-vitro prostate contractility in mature mice. Eur J Pharmacol 2008; 592:151-7; PMID:18655781; http://dx.doi.org/10.1016/j.ejphar.2008.07.003
72. Preston A, Lau WA, Pennefather JN, Ventura S. Effects of adenine nucleosides and nucleotides on neuromuscular transmission to the prostatic stroma of the rat. Br J Pharmacol 2000; 131:1073-80; PMID:11082113; http://dx.doi.org/10.1038/sj.bjp.0703652
73. Preston A, Frydenberg M, Haynes JM. A1 and A2A adenosine receptor modulation of alpha 1-adrenoceptor-mediated contractility in human cultured prostatic stromal cells. Br J Pharmacol 2004; 141:302-10; PMID:14751869; http://dx.doi.org/10.1038/sj.bjp.0705535
74. Pennefather JN, Lau WAK, Mitchelson F, Ventura S. The autonomic and sensory innervation of the smooth muscle of the prostate gland: a review of pharmacological and histological studies. J Auton Pharmacol 2000; 20:193-206; PMID:11260358; http://dx.doi.org/10.1046/j.1365-2680.2000.00195.x
75. Wanigasekara Y, Kepper ME, Keast JR. Immunohistochemical characterisation of pelvic autonomic ganglia in male mice. Cell Tissue Res 2003; 311:175-85; PMID:12596037
76. Davis B, Goepel M, Bein S, Chess-Williams R, Chapple CR, Michel MC. Lack of neuropeptide Y receptor detection in human bladder and prostate. BJU Int 2000; 85:918-24; PMID:10792177; http://dx.doi.org/10.1046/j.1464-410x.2000.00573.x
77. Kopp J, Zhang X, Hökfelt T. Neuropeptide Y1 receptors in the rat genital tract. Regul Pept 1997; 70:149-60; PMID:9272627; http://dx.doi.org/10.1016/S0167-0115(97)00028-1
78. Watts SW, Cohen ML. Effect of bombesin, bradykinin, substance P and CGRP in prostate, bladder body and neck. Peptides 1991; 12:1057-62; PMID:1724795; http://dx.doi.org/10.1016/0196-9781(91)90060-3
79. Ruscica M, Dozio E, Boghossian S, Bovo G, Martos Riaño V, Motta M, et al. Activation of the Y1 receptor by neuropeptide Y regulates the growth of prostate cancer cells. Endocrinology 2006; 147:1466-73; PMID:16339211; http://dx.doi.org/10.1210/en.2005-0925
80. Hedlund P, Ekström P, Larsson B, Alm P, Andersson KE. Heme oxygenase and NO-synthase in the human prostate--relation to adrenergic, cholinergic and peptide-containing nerves. J Auton Nerv Syst 1997; 63:115-26; PMID:9138243; http://dx.doi.org/10.1016/S0165-1838(96)00139-7
81. Juarranz MG, De Neef P, Robberecht P. Vasoactive intestinal polypeptide receptor VPAC(1) subtype is predominant in rat prostate membranes. Prostate 1999; 41:1-6; PMID:10440869; http://dx.doi.org/10.1002/(SICI)1097-0045(19990915)41:1<1::AID-PROS1>3.0.CO;2-A
82. Smith ER, Miller TB, Wilson MM, Appel MC. Effects of vasoactive intestinal peptide on canine prostatic contraction and secretion. Am J Physiol 1984; 247:R701-8; PMID:6388351
83. Crowe R, Chapple CR, Burnstock G. The human prostate gland: a histochemical and immunohistochemical study of neuropeptides, serotonin, dopamine beta-hydroxylase and acetylcholinesterase in autonomic nerves and ganglia. Br J Urol 1991; 68:53-61; PMID:1873692; http://dx.doi.org/10.1111/j.1464-410X.1991.tb15257.x
84. Jen PYP, Dixon JS, Gearhart JP, Gosling JA. Nitric oxide synthase and tyrosine hydroxylase are colocalized in nerves supplying the postnatal human male genitourinary organs. J Urol 1996; 155:1117-21; PMID:8583576; http://dx.doi.org/10.1016/S0022-5347(01)66403-6
85. Walden PD, Marinese D, Srinivasan D, Tzoumaka E, Syyong HT, Ford AP, et al. Effect of neurokinins on canine prostate cell physiology. Prostate 2005; 63:358-68; PMID:15611996; http://dx.doi.org/10.1002/pros.20195
86. Abrahamsson PA, Dizeyi N, Alm P, di Sant'Agnese PA, Deftos LJ, Aumüller G. Calcitonin and calcitonin gene-related peptide in the human prostate gland. Prostate 2000; 44:181-6; PMID:10906733; http://dx.doi.org/10.1002/1097-0045(20000801)44:3<181::AID-PROS1>3.0.CO;2-L
87. Ventura S, Lau WAK, Buljubasich S, Pennefather JN. Calcitonin gene-related peptide (CGRP) inhibits contractions of the prostatic stroma of the rat but not the guinea-pig. Regul Pept 2000; 91:63-73; PMID:10967202; http://dx.doi.org/10.1016/S0167-0115(00)00118-X
88. Arciszewski MB. Distribution of calcitonin gene-related peptide (CGRP), substance P (SP) and galanin (GAL) immunoreactive nerve fibers in the seminal vesicle and prostate of the male sheep. Ann Anat 2004; 186:83-7; PMID:14994916; http://dx.doi.org/10.1016/S0940-9602(04)80130-4
89. Crowe R, Milner P, Lincoln J, Burnstock G. Histochemical and biochemical investigation of adrenergic, cholinergic and peptidergic innervation of the rat ventral prostate 8 weeks after streptozotocin-induced diabetes. J Auton Nerv Syst 1987; 20:103-12; PMID:2444638; http://dx.doi.org/10.1016/0165-1838(87)90107-X
90. Buljubasich S, Lau WA, Pennefather JN, Ventura S. An immunohistochemical and pharmacological study of tachykinins in the rat and guinea-pig prostate glands. Eur J Pharmacol 1999; 380:137-44; PMID:10513573; http://dx.doi.org/10.1016/S0014-2999(99)00524-5
91. Palea S, Corsi M, Artibani W, Ostardo E, Pietra C. Pharmacological characterization of tachykinin NK2 receptors on isolated human urinary bladder, prostatic urethra and prostate. J Pharmacol Exp Ther 1996; 277:700-5; PMID:8627548
92. Burnett AL, Maguire MP, Chamness SL, Ricker DD, Takeda M, Lepor H, et al. Characterization and localization of nitric oxide synthase in the human prostate. Urology 1995; 45:435-9; PMID:7533455; http://dx.doi.org/10.1016/S0090-4295(99)80012-0
93. Takeda M, Tang R, Shapiro E, Burnett AL, Lepor H. Effects of nitric oxide on human and canine prostates. Urology 1995; 45:440-6; PMID:7879335; http://dx.doi.org/10.1016/S0090-4295(99)80013-2
94. Aikawa K, Yokota T, Okamura H, Yamaguchi O. Endogenous nitric oxide-mediated relaxation and nitrinergic innervation in the rabbit prostate: the changes with aging. Prostate 2001; 48:40-6; PMID:11391685; http://dx.doi.org/10.1002/pros.1079
95. Uckert S, Küthe A, Jonas UDO, Stief CG. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001; 166:2484-90; PMID:11696815; http://dx.doi.org/10.1016/S0022-5347(05)65621-2
96. Chow PH, Dockery P, Cheung A. Innervation of accessory sex glands in the adult male golden hamster and quantitative changes of nerve densities with age. Andrologia 1997; 29:331-42; PMID:9430439; http://dx.doi.org/10.1111/j.1439-0272.1997.tb00327.x
97. Moriyama N, Yamaguchi T, Takeuchi T, Sakamoto E, Ueki T, Tsujimoto G, et al. Semiquantitative evaluation of α_{1A}-adrenoceptor subtype mRNA in human hypertrophied and non-hypertrophied prostates: Regional comparison. Life Sci 1998; 64:201-10; http://dx.doi.org/10.1016/S0024-3205(98)00552-9
98. Kojima Y, Sasaki S, Shinoura H, Hayashi Y, Tsujimoto G, Kohri K. Quantification of alpha1-adrenoceptor subtypes by real-time RT-PCR and correlation with age and prostate volume in benign prostatic hyperplasia patients. Prostate 2006; 66:761-7; PMID:16425183; http://dx.doi.org/10.1002/pros.20399
99. Yono M, Foster HE Jr., Weiss RM, Latifpour J. Age related changes in the functional, biochemical and molecular properties of α_1-adrenoceptors in the rat genitourinary tract. J Urol 2006; 176:1214-9; PMID:16890728; http://dx.doi.org/10.1016/j.juro.2006.04.038
100. Quinn R. Comparing rat's to human's age: how old is my rat in people years? Nutrition 2005; 21:775-7; PMID:15925305; http://dx.doi.org/10.1016/j.nut.2005.04.002
101. Frisbie JH, Kumar S, Aguilera EJ, Yalla S. Prostate atrophy and spinal cord lesions. Spinal Cord 2006; 44:24-7; PMID:16010271; http://dx.doi.org/10.1038/sj.sc.3101804
102. Justulin LA Jr., Delella FK, Felisbino SL. Doxazosin reduces cell proliferation and increases collagen fibers in rat prostatic lobes. Cell Tissue Res 2008; 332:171-83; PMID:18188599; http://dx.doi.org/10.1007/s00441-007-0559-3
103. Kojima Y, Sasaki S, Oda N, Koshimizu TA, Hayashi Y, Kiniwa M, et al. Prostate growth inhibition by subtype-selective alpha(1)-adrenoceptor antagonist naftopidil in benign prostatic hyperplasia. Prostate 2009; 69:1521-8; PMID:19544328; http://dx.doi.org/10.1002/pros.21003
104. Mitropoulos D, Kyroudi-Voulgari A, Christelli E, Zervas A, Karayannacos P. Terazosin treatment suppresses basic fibroblast growth factor expression in the rat ventral prostate. Clin Invest Med 2009; 32:E1-7; PMID:19178873
105. Lepor H, Berry SJ. Decreased prostatic secretory function in canine benign prostatic hyperplasia is not due to decreased levels of muscarinic cholinergic receptors. J Urol 1984; 131:803-5; PMID:6200613
106. Kondo S, Tashima Y, Morita T. Adrenergic and cholinergic muscarinic receptors in the prostate of young and old rabbits. Urol Int 1992; 49:201-5; PMID:1335627; http://dx.doi.org/10.1159/000282426
107. Saito M, Kazuyama E, Shimizu S, Dimitriadis F, Kinoshita Y, Masuda E, et al. Muscarinic receptors and their mRNAs in type 2 Goto-Kakizaki diabetic rat prostate. Prostate 2010; 70:1533-9; PMID:20687226; http://dx.doi.org/10.1002/pros.21188
108. Chen C, Ishikawa Y, Amano I, Eguchi T, Ishida H. Age-dependent changes in response of rat prostatic tissues to isoproterenol and forskolin: changes with sexual maturation in function of G proteins. Mech Ageing Dev 1995; 81:1-13; PMID:7475348; http://dx.doi.org/10.1016/0047-6374(94)01577-9
109. Dey A, Lang RJ, Exintaris B. Nitric oxide signaling pathways involved in the inhibition of spontaneous activity in the guinea pig prostate. J Urol 2012; 187:2254-60; PMID:22503041; http://dx.doi.org/10.1016/j.juro.2012.01.072

110. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al.; Standardisation Sub-committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21:167-78; PMID:11857671; http://dx.doi.org/10.1002/nau.10052
111. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol 2003; 44:637-49; PMID:14644114; http://dx.doi.org/10.1016/j.eururo.2003.08.015
112. Barry MJ. Evaluation of symptoms and quality of life in men with benign prostatic hyperplasia. Urology 2001; 58(Suppl 1):25-32, discussion 32; PMID:11750246; http://dx.doi.org/10.1016/S0090-4295(01)01300-0
113. Chapple CR, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. Eur Urol 2006; 49:651-8; PMID:16530611; http://dx.doi.org/10.1016/j.eururo.2006.02.018
114. Kirby RS, Kirby M, Fitzpatrick JM. Benign prostatic hyperplasia: counting the cost of its management. BJU Int 2010; 105:901-2; PMID:20356323; http://dx.doi.org/10.1111/j.1464-410X.2010.09274.x
115. McNeal JE. Origin and evolution of benign prostatic enlargement. Invest Urol 1978; 15:340-5; PMID:75197
116. Bartsch G, Müller HR, Oberholzer M, Rohr HP. Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. J Urol 1979; 122:487-91; PMID:90177
117. Dmochowski RR. Bladder outlet obstruction: etiology and evaluation. Rev Urol 2005; 7(Suppl 6):S3-13; PMID:16986027
118. Lepor H. Pathophysiology of lower urinary tract symptoms in the aging male population. Rev Urol 2005; 7(Suppl 7):S3-11; PMID:16986059
119. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. Eur Urol 2008; 54:419-26; PMID:18325657; http://dx.doi.org/10.1016/j.eururo.2008.02.017
120. Yamada S, Ashizawa N, Ushijima H, Nakayama K, Hayashi E, Honda K. Alpha-1 adrenoceptors in human prostate: characterization and alteration in benign prostatic hypertrophy. J Pharmacol Exp Ther 1987; 242:326-30; PMID:2441028
121. Haynes JM, Ventura S. Current models of human prostate contractility. Clin Exp Pharmacol Physiol 2005; 32:797-804; PMID:16173939; http://dx.doi.org/10.1111/j.1440-1681.2005.04268.x
122. Ventura S, Oliver Vl, White CW, Xie JH, Haynes JM, Exintaris B. Novel drug targets for the pharmacotherapy of benign prostatic hyperplasia (BPH). Br J Pharmacol 2011; 163:891-907; PMID:21410684; http://dx.doi.org/10.1111/j.1476-5381.2011.01332.x
123. Song W, Yuan M, Zhao S. Variation of M3 muscarinic receptor expression in different prostate tissues and its significance. Saudi Med J 2009; 30:1010-6; PMID:19668880
124. Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. Nat Rev Cancer 2005; 5:21-8; PMID:15630412; http://dx.doi.org/10.1038/nrc1528
125. Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr., Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351:1513-20; PMID:15470214; http://dx.doi.org/10.1056/NEJMoa041318
126. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al.; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351:1502-12; PMID:15470213; http://dx.doi.org/10.1056/NEJMoa040720
127. Kyprianou N, Litvak JP, Borkowski A, Alexander R, Jacobs SC. Induction of prostate apoptosis by doxazosin in benign prostatic hyperplasia. J Urol 1998; 159:1810-5; PMID:9598465; http://dx.doi.org/10.1016/S0022-5347(01)63162-8
128. Giardinà D, Martarelli D, Sagratini G, Angeli P, Ballinari D, Gulini U, et al. Doxazosin-related alpha1-adrenoceptor antagonists with prostate antitumor activity. J Med Chem 2009; 52:4951-4; PMID:19719240; http://dx.doi.org/10.1021/jm8016046
129. Liu CM, Lo YC, Tai MH, Wu BN, Wu WJ, Chou YH, et al. Piperazine-designed alpha 1A/alpha 1D-adrenoceptor blocker KMUP-1 and doxazosin provide down-regulation of androgen receptor and PSA in prostatic LNCaP cells growth and specifically in xenografts. Prostate 2009; 69:610-23; PMID:19143029; http://dx.doi.org/10.1002/pros.20919
130. Tahmatzopoulos A, Rowland RG, Kyprianou N. The role of alpha-blockers in the management of prostate cancer. Expert Opin Pharmacother 2004; 5:1279-85; PMID:15163273; http://dx.doi.org/10.1517/14656566.5.6.1279
131. Haynes JM, Frydenberg M, Majewski H. Testosterone- and phorbol ester-stimulated proliferation in human cultured prostatic stromal cells. Cell Signal 2001; 13:703-9; PMID:11602180; http://dx.doi.org/10.1016/S0898-6568(01)00205-4
132. Masur K, Niggemann B, Zanker KS, Entschladen F. Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. Cancer Res 2001; 61:2866-9; PMID:11306460
133. Palm D, Lang K, Niggemann B, Drell TL 4th, Masur K, Zaenker KS, et al. The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by beta-blockers. Int J Cancer 2006; 118:2744-9; PMID:16381019; http://dx.doi.org/10.1002/ijc.21723
134. Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, et al. Behavioral stress accelerates prostate cancer development in mice. J Clin Invest 2013; 123:874-86; PMID:23348742
135. Rayford W, Noble MJ, Austenfeld MA, Weigel J, Mebust WK, Shah GV. Muscarinic cholinergic receptors promote growth of human prostate cancer cells. Prostate 1997; 30:160-6; PMID:9122040; http://dx.doi.org/10.1002/(SICI)1097-0045(19970215)30:3<160::AID-PROS3>3.0.CO;2-Q
136. Batra S, Christensson PI, Hartley-Asp B. Characterization of muscarinic cholinergic receptors in membrane preparations from rat prostatic adenocarcinoma. Prostate 1990; 17:261-8; PMID:2251221; http://dx.doi.org/10.1002/pros.2990170402
137. Rao J, Yang J, Liu Z, Wang L, Yin Z, Liu L, et al. Hypothetic association between greater sympathetic activity and prostate cancer. Med Hypotheses 2008; 71:442-3; PMID:18472228; http://dx.doi.org/10.1016/j.mehy.2008.03.039
138. Esler M, Rumantir M, Kaye D, Lambert G. The sympathetic neurobiology of essential hypertension: disparate influences of obesity, stress, and noradrenaline transporter dysfunction? Am J Hypertens 2001; 14:139S-46S; PMID:11411749; http://dx.doi.org/10.1016/S0895-7061(01)02081-7
139. Moyad MA. Is obesity a risk factor for prostate cancer, and does it even matter? A hypothesis and different perspective. Urology 2002; 59(Suppl 1):41-50; PMID:11937435; http://dx.doi.org/10.1016/S0090-4295(01)01175-X
140. Gann PH, Daviglus ML, Dyer AR, Stamler J. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer Epidemiol Biomarkers Prev 1995; 4:611-6; PMID:8547827
141. Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL. Hypertension, heart rate, use of antihypertensives, and incident prostate cancer. Ann Epidemiol 2001; 11:534-42; PMID:11709272; http://dx.doi.org/10.1016/S1047-2797(01)00246-0
142. Mortensen PB. Neuroleptic medication and reduced risk of prostate cancer in schizophrenic patients. Acta Psychiatr Scand 1992; 85:390-3; PMID:1351334; http://dx.doi.org/10.1111/j.1600-0447.1992.tb10325.x
143. Rosenberg DJ, Neugut AI, Ahsan H, Shea S. Diabetes mellitus and the risk of prostate cancer. Cancer Invest 2002; 20:157-65; PMID:11901534; http://dx.doi.org/10.1081/CNV-120001141
144. Scott PA Sr., Perkash I, Mode D, Wolfe VA, Terris MK. Prostate cancer diagnosed in spinal cord-injured patients is more commonly advanced stage than in able-bodied patients. Urology 2004; 63:509-12; PMID:15028447; http://dx.doi.org/10.1016/j.urology.2003.10.022
145. Perron L, Bairati I, Harel F, Meyer F. Antihypertensive drug use and the risk of prostate cancer (Canada). Cancer Causes Control 2004; 15:535-41; PMID:15280632; http://dx.doi.org/10.1023/B:CACO.0000036152.58271.5e
146. Harris AM, Warner BW, Wilson JM, Becker A, Rowland RG, Conner W, et al. Effect of alpha1-adrenoceptor antagonist exposure on prostate cancer incidence: an observational cohort study. J Urol 2007; 178:2176-80; PMID:17870114; http://dx.doi.org/10.1016/j.juro.2007.06.043
147. Murtola TJ, Tammela TL, Määttänen L, Ala-Opas M, Stenman UH, Auvinen A. Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial. Br J Cancer 2009; 101:843-8; PMID:19654575; http://dx.doi.org/10.1038/sj.bjc.6605188
148. Ramsköld D, Luo S, Wang YC, Li R, Deng Q, Faridani OR, et al. Full-length mRNA-Seq from single-cell levels of RNA and individual circulating tumor cells. Nat Biotechnol 2012; 30:777-82; PMID:22820318; http://dx.doi.org/10.1038/nbt.2282
149. Thebault S, Roudbaraki M, Sydorenko V, Shuba Y, Lemonnier L, Slomianny C, et al. Alpha1-adrenergic receptors activate Ca(2+)-permeable cationic channels in prostate cancer epithelial cells. J Clin Invest 2003; 111:1691-701; PMID:12782672
150. Katsogiannou M, El Boustany C, Gackiere F, Delcourt P, Athias A, Mariot P, et al. Caveolae contribute to the apoptosis resistance induced by the alpha(1A)-adrenoceptor in androgen-independent prostate cancer cells. PLoS One 2009; 4:e7068; PMID:19763272; http://dx.doi.org/10.1371/journal.pone.0007068
151. Jensen BC, Swigart PM, Simpson PC. Ten commercial antibodies for alpha-1-adrenergic receptor subtypes are nonspecific. Naunyn Schmiedebergs Arch Pharmacol 2009; 379:409-12; PMID:18989658; http://dx.doi.org/10.1007/s00210-008-0368-6