



Opening the floodgates: Benign prostatic hyperplasia may represent another disease in the compendium of ailments caused by the global sympathetic bias that emerges with aging

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Summary We have previously posited that the global sympathetic bias that emerges with aging may constitute the common etiologic thread that links a myriad of ailments associated with aging. Recent data suggests that benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) may also be caused by sympathetic bias as an independent etiology from androgen dysfunction. The association of BPH with heart disease, independent of other variables, supports the view that both entities represent downstream manifestations of global sympathetic bias. The risk for development of BPH increases with caffeine intake and decreases with alcohol consumption, factors which wield opposing effects on autonomic balance. Heavy smoking, which induces chronic sympathetic bias, also increases the risk of BPH, a link also previously attributed to hormonal alterations. Sympathetic dysfunction appears to have a mitogenic effect on the prostate. The high prevalence of prostate cancer, a condition detected in the autopsy of many elderly men, may arise from this activity combined with a Th2 shift induced by sympathetic bias, leading to decreased cancer surveillance by the immune system. Exercise may improve BPH by restoring autonomic balance and normalizing the sympathovagal ratio. The benefits of alpha-adrenergic blockers on BPH, generally felt to achieve symptomatic relief afforded by bladder wall and sphincter remodeling, may independently exert a direct effect on prostate growth and enlargement. Sympathetic bias may play a role in adaptive enlargement of other organs such as the salivary glands, heart, liver, spleen, and skeletal muscles in response to stress. We envision novel pharmacologic and device-based neuromodulation therapies for BPH and related urologic dysfunctions based on these principles.

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Introduction

Androgen dysfunction is currently a leading hypothesis in the pathogenesis of benign prostatic hyperplasia (BPH), a common condition among elderly men. We propose that BPH represents another en-

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tity in the constellation of diseases incited by the progressive autonomic imbalance that develops with age.

Evidence

Global sympathetic bias may constitute the common etiologic thread that links many diseases associated with aging [1]. Recent data suggests that BPH and associated lower urinary tract symptoms (LUTS) may also be associated with sympathetic bias [2]. The association of BPH with heart disease, independent of other variables, supports the view that both entities represent downstream manifestations of global sympathetic bias [3–5]. The risk for development of BPH increases with caffeine intake and decreases with alcohol consumption [6]. Caffeine intake notably increases sympathetic bias, whereas alcohol decreases it – findings which support the etiologic role of sympathetic bias. Heavy smoking also induces chronic sympathetic bias [7] and accordingly increases the risk of BPH, a link also previously attributed to hormonal alterations [8,9].

Sympathetic dysfunction appears to have a mitogenic effect on the prostate. Prostate tissue remodeling in the transition zone is specifically characterized by altered autonomic innervation that decreases relaxation and leads to a high adrenergic tone [10]. Studies in rat models have shown that unilateral sympathectomy produces shrinkage as well as a decrease in DNA and protein content on the lesioned side of the prostate. This finding suggests that sympathetic bias may indeed promote prostatic hyperplasia. Accordingly, parasympathectomy produces enlargement as well as an increase in DNA and protein content [11]. Similar observations have been made elsewhere, suggesting that this phenomenon is not restricted to a particular animal model [12].

Implications

The very high prevalence of prostate cancer, a condition detected in the autopsy of many elderly men [13], may relate in part to sympathetically heightened mitogenic activity increasing the stochastic potential for malignant transformation. Prostate cancer may also become predisposed via a Th2 shift induced by sympathetic bias [5], leading to impaired immune surveillance, a condition that the tumor may then subsequently perpetuate [14]. The Th2 shift, growth-promoting effects, angiogenesis, and mitogenic effects associated with sympathetic activity suggest that adrenergic dysfunction

may play a pathogenic role, not just in prostate cancer, but in all cancers.

Recent reports suggest that sympathetic bias may also contribute to the enlargement of other organs, notably the heart [15]. Autonomic denervation and administration of adrenergic antagonists have also been shown to inhibit activity related hyperplasia of salivary glands [16,17]. The findings with the prostate may occur with other glandular and nonglandular tissues, suggesting that autonomic balance may exert a more granular influence than one might first expect, proving essential for regulating cell size and proliferation as much as it does overall organ and system function. Sympathetic bias may play a role in adaptive enlargement of other organs such as the liver, spleen, and skeletal muscles in response to stress.

Exercise may improve BPH by normalizing the sympathovagal ratio [3,18]. In similar fashion, the benefits of alpha-adrenergic blockers on BPH, generally felt to achieve symptomatic relief afforded by bladder wall and sphincter remodeling, may in fact exert a direct effect on prostate growth and enlargement by restoring autonomic balance. We envision novel pharmacologic and device-based neuromodulation therapies for BPH and related urologic dysfunctions based on these principles.

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