Role of insulin and testosterone in prostatic growth: Who is doing what?

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ABSTRACT

Previous studies have demonstrated increased incidence of benign prostatic hyperplasia in insulin-resistant individuals. In addition to androgens, prostatic growth is sensitive to the peptide growth factors including insulin. Experimental studies employing intervention of selective β-cell toxin streptozotocin and castration suggest that depletion of either insulin or testosterone results in the severe prostatic atrophy (>80%). Exogenous testosterone and diet-induced experimental hyperinsulinemia induces prostatic enlargement in rats. Further, hyperinsulinemia sensitizes prostate towards the growth promoting effect of testosterone, and testosterone augments prostatic growth even in the hypoinsulinemic rats. However, in castrated rats diet-induced hyperinsulinemia fails to promote prostatic growth. Based on these evidences it is hypothesized that in the presence of testosterone insulin plays an important role in the prostatic growth. The epidemiological reports witnessing increased incidences of prostatic enlargement in men with metabolic syndrome, which are known to have increased level of insulin, provides a validating clue to the hypothesis. Further, the hypothesis suggests that targeting insulin signaling pathway could be a new objective for the treatment of prostatic enlargement.

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Introduction

Benign prostatic hyperplasia (BPH) is a common problem of the aged men population [1]. It is associated with increase in the contractility and/or enlargement of the prostate gland. About 60% of men aged over 50 years have histological evidence of BPH [1]. Today prostatic hyperplasia is the 4th most prevalent disease in the men aged over 50 years [2]. Although, very few studies have been conducted to examine the prevalence of BPH in India, it was found to be in parallel to that of Western countries [3,4]. Despite the high prevalence in the aged men population, the underlying molecular mechanisms for the pathogenesis of BPH is far from complete understanding. Androgens have long been implicated in the prostatic growth, and are known to play an important role in the pathogenesis of BPH. In addition to the androgens, prostatic growth is sensitive to the peptide growth factors such as transforming growth factors, epithelial growth factor, insulin like growth factor, growth hormone and insulin. The increased incidence of BPH in the insulin-resistant individuals has drawn the attention of scientific community to the growth promoting effects of insulin [5]. Experimental hypoinsulinemia and castration causes dramatic decrease in the weight of the prostate gland. However, diet-induced hyperinsulinemia causes increase in the cellular proliferation and the enlargement of the prostate gland. Further, castration leads to the atrophy of the prostate gland in hyperinsulinemic rats [6] and insulin delays castration associated increased apoptosis in the prostate of diabetic rats [7]. Furthermore, diet rich in saturated fat affects the expression of androgen receptor, alpha-adrenergic receptor, peroxisome proliferators-activated receptor-gamma (PPARγ) in the prostate gland and sensitizes the gland to the growth promoting effects of testosterone [8,9]. Recently Fan et al. reported that insulin like growth factor-1/insulin signaling activates androgen signaling through direct interaction of Foxo-1 with androgen receptor [10]. Based on the experimental and clinical evidences, it was hypothesized that in the presence of testosterone insulin plays an important role in the prostatic growth.

Hypothesis

Experimental evidences

Depletion of either testosterone (by castration) or insulin (by β-cell selective toxin streptozotocin) results in the remarkable decrease in the weight of prostate gland in rodents. However, at normal level of testosterone or insulin, hyperinsulinemia (induced by high-fat diet feeding) and at normal serum concentration of insulin, hypertestosteronemia (by exogenous administration of testosterone) leads to prostatic enlargement. Hyperinsulinemic condition further augments testosterone induced enlargement of the prostate gland. However, hyperinsulinemia fails to promote
prostatic growth in the castrated rats (Table 1). Further, organ culture experiments suggest that presence of both testosterone and insulin promotes the nucleic acid (DNA, RNA) and protein synthesis and best maintains the prostatic cellular integrity then testosterone or insulin alone [11–13], and presence of insulin is required for the full restorative effect of testosterone on the prostate of castrated rats [14].

**Integration of evidences and presentation of the hypothesis**

Based upon these experimental evidences it can be concluded that (i) testosterone as well as insulin is having prostate growth promoting effects, (ii) presence of testosterone is essential for insulin mediated enlargement of the prostate gland, (iii) in hyperinsulinemic rats synergistic increase in the prostate growth is observed in response to the testosterone, (iv) increased level of testosterone can promote prostatic growth even under hypoinsulinemic condition. The phenomenon is depicted with the help of an analogy in Fig. 1. These observations are potentially important since epidemiological data suggests increased incidence of BPH in insulin-resistant individuals and provides an explanation for the prostatic enlargement in men with hypogonadism.

**Limitations and assumptions**

Effect of different experimental condition on the prostate weight and biochemical parameters were derived from different studies, where animals of different age and strain have been utilized. To overcome the biasness or faulty conclusions, which might result due to the inter-experimental variations, at least 25% increase or decrease as compared to control value of the referred experiment in the estimation of the level of testosterone or insulin was considered as high or low respectively. Similarly, in case of prostate size, at least 15% increase or decrease in the weight of prostate gland as compared to that of age matched control group of the referred study was considered as larger or smaller, respectively.

**Table 1**  
Effect of different experimental condition/intervention on the testosterone and insulin level and subsequent effect on the prostate gland.

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Experimental condition/intervention</th>
<th>Level of testosterone</th>
<th>Level of insulin</th>
<th>Prostatic growth</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>[9,27,29,51]</td>
</tr>
<tr>
<td>2</td>
<td>Castration</td>
<td>Low</td>
<td>Normal</td>
<td>Smaller</td>
<td>[52–54]</td>
</tr>
<tr>
<td>3</td>
<td>Streptozotocin treatment</td>
<td>Normal or sub-normal</td>
<td>Normal</td>
<td>Smaller</td>
<td>[27–31,51]</td>
</tr>
<tr>
<td>4</td>
<td>Testosterone administration</td>
<td>High</td>
<td>Normal</td>
<td>Larger</td>
<td>[9,55,56]</td>
</tr>
<tr>
<td>5</td>
<td>High-fat diet feeding</td>
<td>Normal</td>
<td>High [9]</td>
<td>Smaller</td>
<td>[9,35]</td>
</tr>
<tr>
<td>6</td>
<td>High-fat diet feeding and testosterone administration</td>
<td>Exogenous administration of testosterone</td>
<td>High</td>
<td>Larger</td>
<td>[9]</td>
</tr>
<tr>
<td>7</td>
<td>High-fat diet feeding followed by castration</td>
<td>Low</td>
<td>High</td>
<td>Smaller</td>
<td>[6]</td>
</tr>
<tr>
<td>8</td>
<td>Streptozotocin treatment and testosterone administration</td>
<td>Exogenous administration of testosterone propionate</td>
<td>Low</td>
<td>Larger</td>
<td>[14]</td>
</tr>
<tr>
<td>9</td>
<td>Streptozotocin treatment and insulin administration</td>
<td>Sub-normal</td>
<td>Exogenous administration of insulin</td>
<td>Larger</td>
<td>[9,30,31,51]</td>
</tr>
</tbody>
</table>

*a* The ‘low’ and ‘high’ was defined by us based on the experimental data presented in the respective literature. High; at least 25% increase from the control value of referred experiment. Low; at least 25% decrease from the control value of referred experiment.

*b* The ‘smaller’ and ‘larger’ was defined by us based on the experimental data presented in the respective literature. Smaller; at least 15% decrease from the control value of the referred experiment. Larger; at least 15% increase from the control value of the referred experiment.

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**Fig. 1.** A hypothetical model depicting the interplay between levels of insulin and testosterone (thickness of the line indicates level of hormone) in the prostatic growth. The present analogy uses levels of hormones as positive and negative potentials, and prostatic growth as glow of the bulb. Key 1 and 2 describes the nature of the influence of insulin and testosterone levels respectively on the prostatic growth. The red double headed arrow in Key 2 indicates the requirement of a minimal level of testosterone to allow the bulb to glow, while the dotted line connection in Key 1 indicates that low level insulin will allow the bulb to glow. With this model we intend to convey the message that (i) threshold level of testosterone (the red double headed arrow in Key 2) is essential for the prostatic growth, (ii) once the threshold level of testosterone is achieved, the increase in the insulin level can promote the prostatic growth, (iii) at very low level of insulin (the continued dash line in Key 1), rise in the testosterone level can promote prostatic growth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Epidemiological and clinical observations

Recently we have reviewed the inter-relationships between different insulin-resistance associated factors and their possible involvement in the pathogenesis of BPH [5]. Several studies indicate increased incidences of prostatic enlargement and surrogate markers of BPH in men with insulin-resistance syndrome [15–19]. Men undergone sex-reversal demonstrates decrease in the cell number as well as atrophy of the prostate gland [20,21]. However, very less information is available about the size of prostate gland in hypoinsulinemic (type 1 diabetes) individuals.

Possible molecular mechanisms

Insulin signaling initiates on its interaction with the receptor, and branches into two main pathways; one is IRS/PI-3 kinase pathway, primarily concerned with the metabolic effects, second is MEK/ERK pathway, mediating gene-expression and growth-stimulating effects of the hormone [22]. Androgen signaling involves binding of testosterone or dihydrotestosterone to the androgen receptors, the agonist-receptor complex interacts with the DNA and stimulates expression of several growth-regulating proteins [23]. Recently Fan et al. reported IGF-1/insulin signaling activates androgen signaling through direct interaction of Foxo 1 with androgen receptor [10]. Further, in a recent study, Srinivasan et al. reported that E6-associated protein, a dual function steroid hormone receptor coactivator and ubiquitin-protein ligase regulates PI-3Kinase-Akt signaling and prostatic growth [24]. The association between increased activity of PI-3Kinase pathway with the enlargement of prostate gland, and activation of androgen-receptor signaling by the insulin signaling through Foxo-1, which is a substrate of PI-3Kinase provide molecular evidence for the synergistic action of insulin and testosterone in the prostatic growth. Further, hyperinsulinemia is a frequently noted condition in the insulin-resistant individuals, which might augment androgen signaling in the prostate through increased inactivation of the Foxo-1 by IRS/PI3-K branch of the insulin signaling. Furthermore, insulin is known to increase the expression of 5-alpha reductase enzyme (mRNA and protein), which is responsible for the conversion of testosterone to dihydrotestosterone (10 times more potent than testosterone) in the granulose cells [25]. However, these aspects remain to be experimentally examined in the prostate gland.

Hypothesis criticism

The hypothesis presented here can be argued basically due to three major drawbacks; (i) lack of transgenic and/or gene knockout study investigating the effect of prostate specific deletion of insulin-receptor and androgen receptor to provide an conclusive support to the hypothesis, (ii) epidemiological findings reporting the size of the prostate gland in type 1 diabetics, and (iii) absence of clinical evidence for the synergistic action of testosterone and insulin on the prostate gland. However, empirical experimental data such as (i) ventral prostate organ culture experiments examining the effect of testosterone and insulin together or alone [11,13,26], (ii) effect of testosterone on the prostate gland in normal and hyperinsulinemic animals [9], (iii) effect of experimental and genetically induced diabetes on the prostate gland [14,27–31] and (iv) epidemiological evidences indicating increased incidences of BPH in insulin-resistant individuals provide strength to the hypothesis [15,16,18]. Further, literature also supports molecular basis for the interaction between insulin and androgen signaling [10,24].

Discussion and implications

The optimal concentration of insulin is essential for the functional integrity of the prostate gland [28], and rise in the circulating concentration of insulin results in the enlargement of prostate gland in vivo [9]. Recently it has been reported that dietary intake of saturated fat causes increased expression of PPARγ and androgen receptor in the prostate of rats. High-fat diet consisting of approximately 30% animal fat (lard) has long been utilized as a standard method of inducing insulin-resistance in experimental animals which is associated with compensatory rise in the insulin level [32–34]. Although, distinct explanations have been provided, several experimental studies indicates the enlargement of ventral prostate in rats kept on diet rich in saturated fat [8,9,35–37]. Animal studies have indicated enhanced MEK/ERK signaling and increased cellular proliferation in the prostate of diet-induced insulin-resistant rats [6,9,38]. In contrast, few studies suggest that dietary fat (fatty acids) can directly affect the prostatic growth [8,37]. However, the reversal of hyperinsulinemia as well as prostatic enlargement in high-fat diet-fed rats with insulin-sensitizer pioglitazone emphasizes that insulin is playing a central role in the prostatic cell proliferation and growth [6,9,38]. Further, long-term (6 week) administration of exogenous insulin in normal (0.75 IU/kg) and STZ induced hypoinsulinemic (4 IU/kg) rats led to increase in the prostate weight [9]. Other laboratories have also reported restoration of ventral prostate weight in the streptozotocin-induced hypoinsulinemic rats with exogenous insulin [27,28,31]. Although, these experiments provide evidence for the role of insulin in the prostatic growth, the possibility of the direct role of fat in the prostatic growth cannot be denied. To clearly discern the role of fat and insulin-resistance associated compensatory hyperinsulinemia in the prostatic growth further studies utilizing genetically engineered model such as prostate specific deletion of insulin-receptor or androgen receptor or PPAR alpha/gamma receptor is required.

In ventral prostate organ culture experiments co-existence of testosterone and insulin has been found to increase the nucleic acid (DNA and RNA) and protein synthesis than testosterone or insulin alone suggesting the synergistic association between testosterone and insulin [11,13,26]. Further, better reversal of diabetes associated prostatic deformations with the simultaneous use of insulin, testosterone and estrogen then any of them alone indicates the importance of the co-existence of insulin with the steroid hormone [39]. However, the presence of estrogen makes it difficult to derive direct interpretations about the nature of interaction between insulin and testosterone. Moreover, few more studies have also provided evidence for the synergistic interaction of testosterone and insulin [12,40]. The recent finding that (i) insulin activates androgen-receptor signaling through Foxo-1 (a substrate of PI-3Kinase) [10], and (ii) enlargement of prostate gland in E6-AP over-expressing cells with increased PI-3Kinase activity [24] provides molecular basis and strengthens the hypothesis of synergistic association between insulin and testosterone in the prostatic growth.

Aging and androgens is largely accepted to play an important role in the etiopathogenesis of BPH [1,41–43]. Massachusetts Male Aging Study showed steady decrease in the serum androgen levels after 40 years of age despite of increase in the prostate volume [44,45]. Several possible explanations such as change in the estrogen/testosterone ratio, expression of androgen receptor and 5α-reductase enzyme and production of dihydrotestosterone has been proposed to explain this phenomenon [46–48]. Synergism between insulin and testosterone provides another possible explanation for the development of BPH in men with hypogonadism (sub-normal level of testosterone). The level of testosterone in hypogonadism
is much higher as compared to the castrate level, which might be sufficient for the insulin to elicit its growth promoting effects. Epidemiological findings have also enumerated insulin-resistance associated compensatory hyperinsulinemia as an important risk factor for the prostatic enlargement [15,16,18]. Further, recent studies indicate the association of metabolic syndrome with prostate gland. However, the presence of testosterone is a pre-requisite condition for insulin to elicit its growth promoting effects. Further, mechanistic investigations employing transgenic animal models can help to better understand the role of insulin in the pathogenesis of BPH.

Currently, pharmacological agents acting on the androgen signaling are the only strategy to control static component of the BPH. However, the socio-psychological side effects such as impotence and loss of libido necessitate a new class of drug for the management of BPH. Screening of new chemical entities which can selectively modulate the insulin signaling in the prostate gland could be new objectives in the new drug development and for the rationale therapeutics of the BPH. Recently a peptide insulin receptor antagonists have been reported [50]. However, its effect on the prostatic growth under hyperinsulinemic condition has not been evaluated. This type of compounds with proper toxicological evaluation and formulation strategies to act selectively in the prostatic gland could be a new pharmacological option for the treatment of BPH patients.

Conflict of interest statement

None declared.

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